# NEUROPSYCHOLOGICAL CORRELATES OF HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL DYSREGULATION IN DEPRESSION

by

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Date: 9/23/88

Approved:

Robert C. Carson, Ph.D., Supervisor

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Psychology in the Graduate School of Duke University

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ABSTRACT

(Psychology-Psychobiology)

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Recent studies in both humans and animals have documented a relationship between elevated levels of cortisol and cognitive dysfunction. Attempts to investigate this association in depressed patients who show abnormalities of hypothalamic-pituitary-adrenocortical (HPA) functioning have produced equivocal results. The main objective of this study was to examine this relationship further in depressed patients, using multiple measures of HPA axis activity.

It was hypothesized that depressed patients with either disturbances in the integrity of feedback mechanisms (DST nonsuppressors) or with hypersecretion of cortisol or adrenocorticotropic hormone (ACTH) would perform more poorly than patients without HPA disturbances on neuropsychological tests that tapped visual-spatial, visual-ideational abilities. To test these hypotheses, detailed ratings of depressive symptomatology and severity, and an array of neuropsychological tests were administered to sixty inpatients with a DSM-III diagnosis of major depression. Basal (plasma cortisol and ACTH, UFC) and dynamic (dexamethasone suppression test [DST]) endocrine measures were used to identify biological subgroups of depressed patients. The results of this study revealed that DST nonsuppressors performed significantly worse than suppressors on tests involving learning, nonverbal memory, manual dexterity, mental sequencing, abstract concept formation, and visual-spatial conceptualization. This finding was independent of morning and afternoon levels of ACTH and pre-dexamethasone plasma cortisol. Although age predictably affected neuropsychological performance, the association between DST response and cognitive

dysfunction was independent of aging effects. Basal UFC predicted DST suppression status with a high degree of accuracy, and elevated UFC was related to the same set of cognitive disturbances as nonsuppressibility. The relationship between suppressor status and cognitive dysfunction, however, was more robust than that between UFC and cognitive dysfunction. Taken together, these findings suggest that cognitive impairment in some depressed patients is not a function of hypercortisolism per se; rather, both HPA dysregulation and cognitive dysfunction appear to be downstream effects of a central disturbance. Studies of hippocampal degeneration due to exposure to glucocorticoids and changes associated with aging provide evidence consistent with this hypothesis.

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*Psychology and psychiatry can illuminate and define for biology the mental functions that need to be studied if we are to have a meaningful and sophisticated understanding of the biology of the human mind.*
*(Kandel, 1979)*

# CHAPTER 1

# INTRODUCTION

## Historical developments linking the HPA system and behavior

The potential association of psychiatric disorders with disturbances of the hypothalamic-pituitary-adrenocortical (HPA) system has been suggested for many years -- in fact, long before the functional activity of this axis was completely understood. As early as 1868 Addison noted the loss of motivation, "languor", and memory impairment associated with damage to the adrenal glands. Cushing (1913) further elaborated on the relationship between "psychic disturbances" and hyperplasia of the "ductless glands", in particular the pituitary and adrenals. These suggestions were subsequently borne out in studies of patients with either endogenously or exogenously altered HPA functioning.

Concurrently over the last 75 years, the influence of psychological state on neuroendocrine functioning has become more clearly delineated. The complicated interaction of autonomic nervous system and hormonal responses in emotional disturbances was highlighted by the experimental work of Cannon (1914, 1929), particularly by his finding that the epinephrine response to stress mobilized the organism

for "fight" or "flight". At that time, however, only the functions of the adrenal medulla were subject to investigation, and the role of the adrenal cortex in response to stress remained unexplored. Involvement of the adrenal cortex in the physiological response to stressful stimuli was established by Selye's (1936a) research in which adrenocortical enlargement and subsequently (1936b), depletion of cortical lipids was found in rats exposed to a variety of noxious stimuli. Out of Cannon's and Selye's broad conceptualization of stress and activation have come a variety of studies that demonstrate that environmental challenges can be a potent factor in altering adrenocortical function. Subsequent studies over the following three decades showed that this HPA response to stress could be elicited by psychological as well as physical stimuli. For example, Thorn, Jenkins, Laidlaw, Goetz, and Reddy (1953) found that adrenocortical activation occurred in the non-physically stressed coxswain as well as in the oarsmen of the Harvard crew team during a race.

Although these early studies seem to provide evidence for a link between endocrine and behavioral disturbances, findings were generally limited by the state of clinical, physiological, and technological knowledge available at the time. These data did, however, suggest the potential value of exploring the nature and extent of HPA dysregulation during periods of emotional arousal and/or affective disturbance. Research in this area paralleled the biochemical revolution in endocrinology in the 1940's and 1950's. With the development of spectrophotometric techniques for the measurement of urinary products of adrenocortical secretion, it became possible to measure directly

urinary, and then plasma cortisol (and related steroids). It soon became apparent that not only HPA endocrinopathies (such as Cushing's or Addison's disease), but also psychological stimuli (such as impending surgery, stressful airplane flights, examinations, and hospitalization or terminal illness in an individual's family) caused transient and generally moderate increases in circulating plasma corticosteroids in most people (Bliss, Migeon, Branch, & Samuels, 1956; Fransson & Gemzell, 1955; Friedman, Mason, & Hamburg, 1963; Price, Thaler, & Mason, 1957).

The most compelling evidence so far of a behavioral/endocrine interaction is that relating hypercortisolism to major affective disorder. The early research in this field (Board, Wadeson, & Persky, 1957; Bridges & Jones, 1966; Bunney, Mason, & Hamburg, 1965; Doig, Mummery, & Wills, 1966; Gibbons & McHugh, 1962) was inconsistent and generally related the marked and protracted elevations in cortisol in depressed patients to the nonspecific stress of psychosis (Board, Wadeson, & Persky, 1957) or the novelty effects of hospitalization (Mason, Sachar, Fishman, Hamburg, & Handlon, 1965). Subsequently though, it became clear that nonspecific stress could not account for the dramatic HPA abnormalities observed in these patients (Brown & Shuey, 1980; Stokes, Stoll, Koslow, Maas, Davis, Swann et al., 1984; Stokes, Stoll, Mattson, & Sollod, 1976). Moreover, depression was also linked with other state-dependent HPA abnormalities, most notably, resistance to dexamethasone suppression (Carroll, Martin, & Davies, 1968; Stokes, 1966, 1972).

In the last 25 years, HPA abnormalities in depressed patients have

been repeatedly investigated, using a variety of endocrine methodologies, research designs, and patient populations. Pituitary-adrenal disinhibition, in particular cortisol hypersecretion and abnormal dexamethasone suppression test (DST) findings, have been consistently demonstrated in approximately 50% of depressed patients, suggesting that HPA dysfunction may be intrinsic to the pathophysiology of some depressive subtypes. The clinical implications of this endocrine phenomenon have not yet emerged, though early escape from dexamethasone suppression has been associated with older age (Asnis, Sachar, Halbreich, Nathan, Novacenko, & Ostrow, 1981; Brown & Qualls, 1981; Georgotas, Stokes, Krakowski, Fanelli, & Cooper, 1984), suicidality (Targum, Rosen, & Capodanno, 1983), both psychomotor agitation (Brown, Stoll, Stokes, Frances, Kocsis, & Mann, in press) and retardation (Asnis et al.,1981), anxiety (Kocsis, Davis, Katz, Koslow, Stokes, Casper, et al., 1985), and absence of significant life events prior to the onset of a depressive episode (Roy, Pickar, Linnoila, Doran, & Paul, 1986). Most studies have failed to find a correlation between abnormal DST results and severity of depression in endogenously depressed patients (i.e., those patients having a particular symptom profile consisting of lack of reactivity, distinct quality of depressed mood, anhedonia, sleep and appetite disturbances, and psychomotor agitation or retardation).

Despite longstanding recognition of cognitive impairment as a feature of depression (Weingartner & Silberman, 1982), there have been relatively few attempts to explore cognitive functioning in relation to HPA dysregulation in depression. This seems unusual, given that

circulating corticosteroids are known to have both direct and indirect effects on the central nervous system (CNS) which could potentially alter cognitive, affective, and psychomotor performance (e.g., Henkin & Daly, 1968; Momose, Kjellberg, & Kliman, 1971). The purpose of the present study is to explore clinical differences between various biologically distinct subgroups of depressed patients (DST suppressors vs. nonsuppressors, urinary free cortisol hypersecretors vs. normosecretors) using detailed measures of affective, cognitive, and psychomotor functioning as the major psychological parameters. Specifically, affective symptoms and neuropsychological deficits will be evaluated in terms of various levels of HPA functioning: (1) baseline measures of cortisol and adrenocorticotropic hormone (ACTH); (2) 24 hour urinary free cortisol (UFC), an integrated measure of HPA activity over time; and (3) abnormalities of feedback inhibition (reflected in the cortisol response to dexamethasone). These measures will enable us to assess whether there is a specificity of psychological/cognitive function relating to a particular endocrine abnormality.

The literature review that follows describes, first, the basic structure and functioning of the HPA system under normal conditions. Although it is not within the scope of this paper to give exhaustive coverage to the vast endocrine and neuroanatomy literature detailing the organization of this axis, the following review briefly summarizes our current understanding of its anatomy and physiology. This will enable the reader to better comprehend subsequent descriptions of HPA functioning in pathological states. A discussion of the dexamethasone

suppression test (DST) and its relationship to various clinical variables will follow. Next, evidence suggesting an association between HPA activation and cognitive dysfunction will be reviewed. Finally, the aims, objectives, and specific hypotheses for the present study will be described.

*My mind sent a message to my hypothalamus, told it to release the hormone CRF into the short vessels connecting my hypothalamus and my pituitary gland. The CRF inspired my pituitary gland to dump the hormone ACTH into my blood stream. My pituitary had been making and storing ACTH for just such an occasion. . . And some of the ACTH in my bloodstream reached the outer shell of my adrenal gland, which had been making and storing glucocorticoids for emergencies. My adrenal gland added the glucocorticoids to my bloodstream. They went all over my body, changing glycogen into glucose.*

*(Kurt Vonnegut, Jr., Breakfast of Champions, 1973)*

HPA anatomy and physiology

The normal adrenal cortex and steroidogenesis.

The adrenal glands are usually located near the upper pole of the kidneys bilaterally (Neville & O'Hare, 1979), and are composed of two separate and distinct endocrine tissues. The cortex comprises about 90% of the gland and surrounds the thin layer of centrally-located medulla. Each cortex is anatomically and functionally segregated into three zones (Robin & McKenna, 1982). The outermost zona glomerulosa is under the control of the renin-angiotensin system and secretes the salt-retaining mineralocorticoid aldosterone. The innermost area, the zona reticularis produces mainly the androgenic steroids such as dehydroepiandrosterone and androstenedione, as well as estrogens and cortisol. The zona fasciculata lies beneath the zona glomerulosa and is the main site of cortisol production, the major glucocorticoid in humans. Other glucocorticoids (corticosterone, deoxycorticosterone, 11-deoxycortisol) are also secreted in much smaller amounts.

The glucocorticoids derive their name from the ability to raise blood sugar levels as a result of promoting gluconeogenesis (Baxter &

Rousseau, 1979). In addition, the glucocorticoids increase the deposition of glycogen in the liver, catabolize protein, and suppress inflammatory and immune reactions (Baxter & Tyrrell, 1985). Glucocorticoids are crucial for the normal day-to-day functioning of humans and other species. In the absence of glucocorticoid secretion (i.e., Addison's disease), the organism cannot withstand the metabolic demands imposed by routine stress, and adrenal crisis results; if appropriate treatment is not instituted, the outcome is usually fatal.

Synthesis of cortisol is accomplished by enzymatic stepwise modification of cholesterol taken up from the blood, or synthesized from acetate within the adrenocortical cells (Brown, Kovanen, & Goldstein, 1979). Cortisol secretion from the adrenal cortex circulates for the greater part bound to plasma proteins (Ballard, 1979; Sandberg & Slaunwhite, 1971; Westphal, 1971). About 75% of this binding is due to a tight, but reversible association of the steroid with corticosteroid-binding globulin (CBG, also known as transcortin). Another 15% is loosely bound to albumin, and about 10% (or somewhat less) is present in plasma as free cortisol. It is this latter portion which is biologically active because it can diffuse easily across the capillary beds of the body, thus bathing all tissue cells. It is likely that free cortisol is the main factor involved in feedback control of ACTH release from the pituitary (Mestman & Nelson, 1963), and effects on glucose metabolism and other metabolic changes associated with hypercortisolism (Zinneman, Seal, & Doe, 1967). At cortisol concentrations below 20 or 25 mcg/dl, the free cortisol in plasma is linearly related to the total cortisol concentration

(Ballard, 1979), however above this level CBG becomes saturated and the relative proportion of free cortisol increases in a non-linear manner.

The metabolism of cortisol is mainly conducted in the liver (Brooks, 1979; Peterson, 1971), and cortisol and its metabolites are then excreted primarily via the urine (Hellman, Bradlow, Frazed, & Gallagher, 1956) as urinary 17-hydroxycorticosteroids (17-OHCS), 17-ketogenic steroids (17-KGS), and as unchanged cortisol. The 17-OHCS account for approximately 50% of the metabolites of cortisol and provide a convenient index of cortisol secretion. The small fraction of cortisol which is unchanged (1%) is called urinary free cortisol, and if renal function is normal, will reflect the levels of circulating non-protein bound cortisol. The 17-KGS refer to a group of steroids obtained by converting susceptible cortisol metabolites to 17-ketosteroids; however, they are also derived from noncortisol metabolites and thus provide only an indirect index of cortisol secretion. When there is excess adrenal secretion of cortisol such that the total capacity of CBG is exceeded, then increasing and elevated amounts of free cortisol in plasma cross the glomerular membrane of the kidneys and are present in the urine.

ACTH regulation of adrenocortical function.

The hypothalamus, pituitary, and adrenals form a neuroendocrine axis whose primary function is to regulate secretion of cortisol and other adrenal steroids. Steroidogenesis and growth of the adrenal cortices is directly dependent upon stimulation by ACTH. Adrenocorticotropin is a 39-amino acid polypeptide secreted from the anterior lobe of the pituitary. The secretion of ACTH, in turn, is

stimulated by corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), and possibly other substances produced primarily in the paraventricular nucleus of the hypothalamus (Krieger & Zimmerman, 1977; Whitnall, Mezey, & Gainer, 1985). CRH and AVP travel through neurons to the median eminence and are secreted into the portal vessels, which carry them to the adenohypophysis. In the anterior pituitary, a large precursor "prohormone", proopiomelanocortin (POMC), undergoes several cleavages that result in the elaboration of beta-lipotropin, ACTH, gamma-lipotropin, endorphins, and enkephalins (Miller, Johnson, Baxter, & Roberts, 1980; Roberts et al., 1979). Steroid release may also be influenced by the innervation of the adrenals and perhaps by other less well understood humoral factors.

ACTH stimulates release of cortisol from the adrenals within 2 to 3 minutes, largely due to increased steroidogenesis (Simpson & Waterman, 1979). Adrenal androgens and other steroids are also released. When ACTH plasma levels fall, steroid biosynthesis rapidly declines. With more prolonged stimulation, total adrenal protein and RNA synthesis increase, leading to hypertrophy with increased adrenal weight and protein-nucleic acid content (Hall, 1985). Within limits, both the magnitude and duration of the adrenal secretory response are linearly related to the dose or level of ACTH.

Extrahypothalamic control of CRH.

CRH is probably the most important overall stimulator of ACTH release. The hypothalamic neurosecretory cells which release CRH receive neural inputs from a variety of pathways utilizing a particular neurotransmitter. Several neurotransmitter substances and pathways,

including serotonergic and cholinergic excitatory pathways, and noradrenergic and possibly gabanergic and other inhibitory pathways appear to be involved (Jones, Gillham, DiRenzo, Beckford, & Holmes, 1981).

Because the hypothalamus is structurally and functionally interconnected with several important brain regions, the median eminence is not exclusively responsible for CNS integration of HPA activity. On the other hand, extrahypothalamic mechanisms do not appear to be necessary for basal HPA activity, because if all pathways to the medial basal hypothalamus are surgically severed in the rat, diurnal rhythm is lost, but plasma corticosterone levels remain elevated and steady (Halasz, Slusher, & Gorski, 1967). Inhibitory feedback receptors have been identified in the limbic system, hippocampus, and in other midbrain centers that have been implicated in the control of emotions and information processing. Additionally, the hypothalamus receives direct neural input from the reticular formation. The role of these extrahypothalamic regions in regulating pituitary function has been inferred from lesion/ablation and stimulation studies. In general, these regulatory areas are those which contain glucocorticoid feedback receptors.

The ascending reticular activating system (ARAS), a region involved in sustaining arousal, appears to have both inhibitory and excitatory influences on the HPA system, which are mediated via different neural pathways (Taylor, 1969). For example, stimulation of the ARAS has been shown to increase ACTH when basal HPA activity is low, and decrease release during periods of HPA activation. Of

particular importance for the study of neural control of the HPA axis is the limbic system. The amygdaloid complex appears to exert a facilitory influence on CRH neurons, because stimulation usually activates ACTH release, whereas bilateral destruction diminishes the activity of the system (Gloor, Murphy, & Dreifuss, 1969; Mangili, Motta, & Martini, 1966; Redgate, 1970; Rubin, Mandell, & Crandall, 1966). This relationship, however, has not held up under a variety of experimental conditions. For example, Ganong (1963) reported that bilateral destruction of the amygdaloid nuclei in the dog reduced the ACTH response to immobilization stress, but not to gut traction. Furthermore, stimulation of the anteromedial amygdala results in HPA activation, whereas identical stimulation of the basolateral amygdala has the opposite effect (Slusher & Hyde, 1961), illustrating the importance of functional localization within each of these extrahypothalamic regions. Finally, HPA activation in response to prolonged amygdaloid stimulation is not sustained, although the system is functionally capable of further response (Sachar et al., 1973).

Hippocampal lesioning results in chronically elevated basal levels of plasma corticosterone (Rubin, Mandell, & Crandall,1966), suggesting a tonic inhibitory influence on HPA activity. However, as with the ARAS, the influence of the hippocampus appears to depend upon the prior functional activity of the HPA system. As an example, the stress-induced release of ACTH is blocked by hippocampal stimulation (Endroczi, Lissak, Bohus, & Kovacs, 1959), but resting pituitary adrenocortical activity is facilitated (Kawakami, Seto, Kimura, & Yanase, 1971). Transection of the fornix, which contains hypothalamic

projections, has been shown to abolish the circadian rhythm of corticosterone secretion in the rat (Moberg, Scapagnini, de Groot, & Ganong, 1971), but this rhythm returns a short time after transection (Lengvari & Halasz, 1973). What emerges from this brief review of extra-hypothalamic regulatory areas is that the hypothalamus serves as the "crossroads" for several major midbrain and limbic pathways. Disturbances in these limbic midbrain circuits may well be implicated in the neuroendocrine, appetitive, and affective changes that occur in major depression.

Regulation of ACTH secretion.

It is now generally accepted that three factors govern the secretion of ACTH by the normal pituitary, and hence control cortisol release. First, endogenous rhythms in the CNS result in pulsatile release of ACTH and cortisol that produce an episodic, circadian, and meal-stimulated pattern. Second, a number of physical and psychological stresses ultimately mediated via the limbic system and reticular formation, can increase ACTH and cortisol release above the spontaneous pattern. Finally, a "set-point" is maintained by long- and short-loop feedback systems. Each factor will be discussed briefly, and some actions describing their interaction will also be summarized.

The currently recognized HPA circadian rhythm, consisting of a series of episodic bursts of ACTH and cortisol release was first described in 1970 by studies in humans (Hellman et al., 1970). The results from subsequent studies indicated that the pattern of pulsatile release of cortisol roughly relates to immediately prior ACTH pulses, although there may be releases of cortisol that are seemingly

independent of ACTH release (Fehm, Klein, Holl, & Voigt, 1984; Krieger, 1979). It should be noted that in normal healthy individuals, a steady-state level of cortisol is not present for any long period during the day, since each burst of cortisol produces a sharp rise in concentration, followed by a slower, generally smooth decline. In general, the pattern of cortisol release shows increasing secretory episodes early in the a.m. hours, with decreasing secretion in the late afternoon and evening in healthy individuals (Weitzman et al., 1971). The increased frequency and duration of the cortisol bursts during the early a.m. hours (just prior to awakening and until about 10 a.m.) results in a gradual accumulation of plasma cortisol due to its prolonged half-life (approximately 60-90 minutes).

The episodic bursts do not occur as a consequence of reduced plasma glucocorticoid levels initiating ACTH secretion. Low plasma levels of cortisol during sleep do not stimulate ACTH secretion, and high levels occurring during the main secretory phase do not suppress continuing ACTH release over the short run. Presumably, then, the pattern of ACTH secretion is intrinsic to the hypothalamic control system and to various CNS oscillators, and is independent of feedback control.

Aside from this general secretory pattern, there is considerable variability in secretory output, duration, and latency of secretory episodes, not only between individuals, but also in a given individual on different days (Weitzman et al., 1971).

The CNS events responsible for the secretory patterns of ACTH and cortisol release are poorly understood, though the phase of this rhythm

appears to be controlled by an oscillator located in the suprachiasmatic nucleus or SCN (Moore, 1981), an area which receives abundant cholinergic and serotonergic input. The SCN is also believed to regulate the periodicity of temperature, eating, drinking, and activity.

The circadian rhythm and responsiveness of the HPA axis seem to be influenced by extrapituitary, non-ACTH mechanisms. The presence of these extrapituitary influences has been suggested by the preservation of plasma corticosteroid rhythms in various species of hypophysectomized animals (Guillemant, Guillemant, & Reinberg, 1980; Srivastava & Meier, 1972). Moreover, the limbic system appears to be intimately related to this rhythm, since fornix transection will temporarily disrupt the circadian rhythm (Moberg, Scapagnini, de Groot, & Ganong, 1971). Disease of the pretectal and temporal lobes of the brain also distorts or obliterates the diurnal rhythm (Krieger, Glick, & Silverberg, 1968). Serotonergic pathways also appear to influence the circadian periodicity of the HPA system. Drugs that inhibit the effects of serotonin (such as cyproheptadine or parachlorphenylalanine) abolish the circadian rhythm in animals (Krieger & Rizzo, 1970; Scapagnini, Moberg, Van Loon, de Groot, & Ganong, 1971). Similarly, cyproheptadine prevents the main secretory phase in humans (Chihara, Kato, & Maeda, 1976). Interestingly, there is a circadian pattern in the CNS content of serotonin which parallels HPA cyclicity, and this serotonin rhythm matures at the same time as the appearance of a diurnal HPA rhythm (Scapagnini, Moberg, Van Loon, de Groot, & Ganong, 1971).

There does not appear to be circadian responsiveness of the pituitary to CRH (Krieger, 1979), and the circadian rhythm of ACTH is preserved when CRH is infused continuously (Brandenberger, 1984; Follenius, Muzet, Simeoni, & Reinhardt, 1984). There is however a circadian periodicity in hypothalamic release of CRH in mammals, which precedes that of ACTH and cortisol by approximately 14 hours (Garrick et al., 1987). Thus, to a significant degree, the ACTH and cortisol rhythms appear to be mediated by factors other than CRH. In addition, aspects of the periodicity involve mechanisms independent of changes in pituitary release. For example, there can be release of cortisol that is not associated with ACTH release and vice versa (Krieger, 1979). In hypophysectomized animals given ACTH infusions, cortisol rhythms persist despite constant ACTH concentrations (Sherman, Wysham, & Pfohl, 1985). Further, in rats, spinal cord transection at T7, but not by lumbar cord section, abolishes the rhythmic response to constant ACTH stimulation in hypophysectomized rats (Allen & Allen, 1975; Ottenweller & Meier, 1982). Hemorrhage in dogs results in identical ACTH response whether the stress is applied in the morning or in the evening, but the cortisol response in the morning is greater than in the evening (Engeland, Byrnes, & Gann, 1982). These data suggest that adrenocortical rhythmicity is mediated by the hypothalamic-pituitary system (via ACTH), and by the direct action of the nervous system.

Although the circadian rhythm of the HPA axis is endogenous, its phase can be entrained by several Zeitgebers. A major Zeitgeber, especially in animals is the light-dark cycle. Phase reversal of this cycle produces phase reversal of plasma ACTH/cortisol secretion. This

effect of light is believed to be mediated by the SCN via the retinohypothalamic pathway (Moore & Lenn, 1972). The rhythm is altered to a persistent low level following protracted continuous light exposure (Cheifetz, Gaffud, & Dingan, 1968), as it is by blindness (Krieger, 1973). Although the influence of food on the overall rhythm has not been documented in humans, episodes of cortisol release do occur after lunch and dinner (Follenius, Brandenberger, Hietter, Simeoni, & Reinhardt, 1983; Goldman et al., 1985). The rhythmicity persists with prolonged bed rest, continuous feeding, and 2 to 3 day periods of sleep deprivation (Krieger, 1979), but is phase-shifted by food and water restrictions (Cheifetz, Gaffud, & Dingan, 1968; Kao, Saito, & Suda, 1980). The diurnal rhythm can be modified by altering the sleep pattern, but only if the change is maintained for several days (Orth, Island, & Liddle, 1967). It remains normal in individuals who work night shifts but maintain a normal weekend lifestyle. If sleep-wake-feeding patterns are totally altered (e.g., moving to a different time zone), then the circadian rhythm also changes, but only after 2 to 3 weeks (Krieger, 1975). Thus, the circadian rhythmicity of the HPA system seems to be multidetermined.

The natural rhythm of cortisol release can be disrupted by a variety of acute physical and psychological stresses, and by a number of chronic conditions. Acute psychological stimuli that result in increased cortisol release can be seemingly mild, such as venipuncture (Davis et al., 1962), or more severe, such as preparation for surgery (Czeister et al., 1976). The stress of hospitalization can lead to cortisol hypersecretion (Mason, 1959), which may be resistant to

glucocorticoid suppression (Connolly, Gore, Stanley, & Wills, 1968). In situations of more prolonged stress, it is more difficult to predict whether cortisol levels will be elevated. The influence of depression upon adrenal activity will be discussed later in this paper. Physical stresses that increase ACTH and cortisol release include severe trauma, major surgery, severe illness, hypoglycemia, fever, burns, cold exposure, hypotension, severe dehydration, irradiation, and moderate to intensive exercise (Baxter & Tyrrell, 1987). The response to moderate acute stress (e.g., hypoglycemia) can be attenuated or even prevented by pretreatment with dexamethasone, which inhibits ACTH release through feedback mechanisms (Copinschi, L'Hermite, & Le Clercq, 1975). The stimulating effect of more severe physical stress (e.g., major surgery) or emotional stress (e.g., dissertation defense) cannot be prevented by pretreatment with a corticosteroid (Estep, Island, & Ney, 1963; Kalin, Cohen, & Kraemer, 1981).

The endocrine response to stress is generally related to the intensity of the stimulus. For example, mild stress (e.g., 24-hour fast) does not increase adrenocortical activity (Arendt, Hampton, & English, 1982), whereas in burn patients, the adrenocortical activation is proportional to the degree and extent of tissue damage (Vaughan, Becker, & Allen, 1982). Under extremely severe stress, the adrenals may fail and plasma cortisol levels will plummet -- a potentially fatal situation (Finley & McKee, 1982).

The HPA axis, like all the neuroendocrine axes, has feedback loops which help to maintain an intrinsic homeostatic system. The feedback regulation of corticotropin secretion in man and especially in animals

has been extensively studied (Daly, Reade, Alaghband-Zadeh, & Haismer, 1979; Keller-Wood & Dallman, 1984). What follows is a brief summary of these findings excerpted from a recent review of HPA anatomy and physiology (Stokes & Sikes, 1987).

Feedback processes in the HPA axis are mainly inhibitory, i.e., the target gland (adrenal cortex) regulates its own secretion (cortisol) by suppressing the release of the corresponding tropic (ACTH) and releasing (CRH) hormones. All available evidence suggests that positive feedback does not play a pivotal role because surgical isolation of the medial basal hypothalamus results in tonic secretion of corticosterone (Halasz, Slusher, & Gorski, 1967). Instead, disinhibition of negative feedback mechanisms occurs when circulating cortisol concentrations decrease. Thus, the corticotropes (pituitary cells that secrete ACTH) are programmed to halt ACTH secretion above a certain "set-point", and resume secretion when corticosteroid concentrations fall below a certain level. The HPA system is essentially a closed-loop system; however, as previously discussed, certain physical and psychological stimuli may enhance or restrict CRH release or modulate feedback processes via alterations in "set-point".

It is now clear that feedback inhibition of ACTH secretion can be separated mechanistically into three components. The first is a fast, rate-sensitive feedback occurring within seconds to minutes of an increase or rise in cortisol. The second type of feedback is "intermediate", and occurs over 2 to 10 hours. The third feedback is termed "delayed" feedback and it takes place some hours to days after corticosteroid administration.

The fast feedback component is transient, lasting less than 10 minutes in some animal species, and is initiated by a sudden increase in glucocorticoid concentration impinging on rate-sensitive mechanisms in the hypothalamus and the pituitary (Fehm, Voigt, Kummer, Lang, & Pfeiffer, 1979; Jones, 1979; Keller-Wood & Dallman, 1984). The hypothalamic effect may be more prominent since in rats the suppression can be overridden by CRH administration (Jones, 1979).

Fast feedback has been extensively studied in rodents, although in humans a decrease in circulating ACTH levels is obvious within 15 minutes (Fehm, Voigt, Kummer, Lang, & Pfeiffer, 1979). In rats, the decrease in ACTH concentrations is detectable within 2 minutes and is not dose-dependent, but is proportional to the rate of increase of the level of glucocorticoid (Jones, 1979; Keller-Wood & Dallman, 1984). During this period, the ACTH response to some stimuli remain blunted (e.g., histamine) but the axis is responsive to more potent stimuli such as surgery (Jones, 1979). The fast feedback occurs too rapidly to be accounted for by the classic glucocorticoid influences on RNA. It appears that initial mechanisms by which corticoids exert a feedback effect involve direct release of CRH and ACTH by actions on the cell membrane (Jones, 1979). The fast feedback response is followed by a 2-hour "silent" period during which feedback is relatively inactive, although certain stressful stimuli may produce ACTH release (Jones, Brush, & Neame, 1972). The silent period ends with the beginning of the intermediate feedback control.

Both intermediate and delayed feedback are progressive, and depend on the total dose of steroid administered over time. They can be

separated mechanistically by a number of factors (Keller-Wood & Dallman, 1984). First, intermediate feedback appears after relatively short periods of exposure to steroids, or after repeated, but discontinuous increases in plasma glucocorticoids. Delayed feedback appears after prolonged exposure to medium or high plasma corticosteroid levels. Second, the intermediate feedback lasts only a few hours, during which time ACTH and CRF release, but not synthesis, are inhibited. After 12 hours of treatment with dexamethasone (delayed feedback), however, there is evidence for decreased mRNA activity in rats (Roberts, Budarf, Baxter, & Herbert, 1979). Thereafter, ACTH production progressively fails and ACTH stores become rapidly depleted in vivo. These two mechanisms also differ in that during the intermediate feedback stage, the axis, although suppressed and unresponsive to certain stimuli, can respond to other stimuli, such as gut traction or severe hemorrhage (Dallman, 1979). With time, the delayed feedback progresses to result in total unresponsiveness of the axis to even extreme stimuli, as is observed in patients with Cushing's syndrome or on long-term, high-dose glucocorticoid therapy. The delayed feedback persists as long as steroid administration continues (Jones, 1979). Following withdrawal of the glucocorticoid there is a return to normal function, however, the recovery period varies with the extent and duration of the suppression, and can be from hours to months (Dallman, 1979; Jones, 1979; Keller-Wood & Dallman, 1984). For example, Liddle et al. (1962) studied the hierarchical recovery of the HPA axis in individuals who had been exposed to chronically high autonomous output from adrenal adenomas. ACTH levels returned to

normal only after 3-6 months, and it was some months thereafter before adrenal cortisol secretion was manifest.

The delayed feedback phase kicks in after several hours and is associated with unresponsiveness to CRH, with marked decreases in POMC mRNA -- a genomic effect (Birnberg, Lissitzky, Hinman, & Herbert, 1983) -- and a decrease in the number of pituitary ACTH-containing cells. The effects on hypothalamic protein synthesis are less severe (Jingami, Matsukara, Numa, & Imura, 1985), although hypothalamic CRH and AVP content are diminished (Suda et al., 1984).

Two important points emerge from this brief review of feedback mechanisms. First, the interpretation of these findings is limited by the fact that feedback has generally been demonstrated by treatment with exogenous glucocorticoids and subsequent measurement of either basal or stimulated activity in the system. Thus, the physiological role of this negative feedback has not been fully discerned. In fact, there is little direct evidence showing fast feedback inhibition to be present in a physiologically relevent manner in humans during conditions of stress. It seems likely, however, that fast and intermediate feedback should occur under physiological conditions in which plasma corticosteroids are produced in response to moderate stress. Delayed feedback, however, would be expected to occur only in pathological conditions or after pharmacological treatment with steroids, when plasma steroid levels are elevated for protracted periods of time. Therefore, under normal conditions, decrease in POMC mRNA synthesis or pituitary ACTH content would not be expected to occur in response to moderate stress.

Finally, the feedback relationship explains why simultaneous assessment of both basal levels and dynamic response of the system is mandatory in the determination of pathological states. In fact, disturbances in feedback mechanisms are almost invariably involved in pathological conditions that perturb endocrine function. Altered feedback inhibition, as determined by the DST, has recently been observed in a number of psychiatric illnesses including major depression, eating disorders, alcoholism, and anxiety disorders. These disturbances and their clinical relevance will be discussed later in this paper.

Summary of mechanisms regulating HPA functioning.

Since the normal adrenal cortex generally secretes cortisol primarily in response to ACTH, the basic factor in determining HPA activity is the secretion of ACTH from the pituitary. The regulation of ACTH secretion is complex and multidetermined. First, the hypothalamus produces both CRH and AVP, which stimulate cyclic AMP formation within ACTH secreting cells. Second, there is growing evidence that limbic structures also modulate baseline levels of ACTH in the general circulation via release of CRH from the hypothalamus by excitatory (e.g., cholinergic) and inhibitory (e.g., noradrenergic) control. Third, cortisol, probably by actions on the pituitary, hypothalamus, and/or limbic system, inhibits ACTH release when plasma glucocorticoid concentrations reach a critical level. In addition, ACTH probably acts at the hypothalamic level to regulate its own secretion. Fourth, there is an innate circadian rhythm of steroid secretion. Fifth, superimposed on all other regulators of ACTH

seceretion is the stimulatory influence of both physical and psychological stress.

HPA disturbances in depression

HPA abnormalities in depressed patients have been detected in a variety of biofluids (plasma, urine, cerebrospinal fluid, saliva) using both basal and challenge (provocation/suppression) paradigms. Each of these methodologies has its relative advantages and disadvantages. Basal measures provide an index of the resting activity of the system at one or multiple time points. Basal measures can be useful in situations where hormone levels are relatively stable due to long plasma half-life (e.g., cortisol). However, the reliability of isolated plasma measurements can suffer from unpredictable episodic release and environmental stresses superimposed on the circadian rhythm as well as from assay variance. Further, because the plasma concentrations of adrenal hormones and ACTH can vary significantly among normal individuals on different days, the information provided may be limited unless hormone levels are grossly abnormal. On the other hand, 24- or 48-hour cannula studies, while partially circumventing these weaknesses, are time-consuming, costly, and too invasive for practical clinical applications. One of the simplest and most informative basal measures of HPA functioning for psychoendocrine research is provided by the measure of 24-hour urinary free cortisol. Assuming that urine collection is complete (and this can be determined based on the relative constancy of urinary creatinine excretion), 24-hour free cortisol provides a fairly reliable estimate of HPA activity

(secretion) over time, and the problems of episodic release with plasma assessments can be bypassed.

Challenge paradigms provide a way of assessing the functional capacity of the system, its reserve capacity, and its ability to respond to perturbations, as well as the integrity of negative feedback mechanisms. These tests enable us to pinpoint more precisely the site(s) of dysregulation. In a neuroendocrine system that incorporates several functionally interdependent organs such as the HPA axis (i.e., the brain with subdivisions of cortex, limbic system, and hypothalamus; pituitary; adrenal cortices), the need for a number of complementary measures is obvious.

Although increased HPA activity involves increased secretion of diverse peptides and hormones under varying conditions, this section will focus exclusively on measurements germane to the study: basal plasma cortisol and ACTH, and urinary free cortisol. The dexamethasone suppression test will be reviewed in the following section.

Basal plasma cortisol.

Disturbance in cortisol secretion is one of the most consistently and extensively reported neuroendocrine abnormalities of depressive illness. Whereas earlier psychoendocrine investigators utilized indirect indices of adrenocortical function such as eosinophil levels or metabolites of adrenocortical hormones (Board, Wadeson, & Persky, 1957; Bunney, Mason, Roatch, & Hamburg, 1965; Mason, 1959), studies in the mid-1960's began focussing on more direct indices such as plasma concentrations of cortisol (Carpenter & Bunney, 1971; Gibbons & McHugh, 1962; Sachar, 1967). The general consensus from these studies is that

cortisol hypersecretion (manifested by increased mean morning and evening plasma cortisol levels, relative flattening of the circadian rhythm, higher secretion rates, and increased number and magnitude of secretory episodes) is found in 40-50% of severely depressed patients. This heightened HPA activity does not appear to be just a nonspecific effect of emotional arousal or hospitalization per se (Gibbons, Gibson, Maxwell, & Wilcox, 1960). In fact, the HPA activation seen in depressed patients is much more protracted, and in general, much greater than that observed in conditions of stress, anticipation, or novelty. Although cortisol hypersecretion in depressed patients was amply documented during the 1960's and early 1970's, these measures were relatively ignored until recently, in part due to widespread interest in the DST.

The phenomenon of cortisol hypersecretion appears to be predominantly a state-related finding, generally normalizing after clinical recovery (Sachar, 1975). The clinical correlates of cortisol hypersecretion have been sought, but remain equivocal. Despite early suggestions of an association with anxiety, psychosis, and severity of illness, these findings have not been consistently replicated. One variable which has been found to be consistently correlated with cortisol hypersecretion in endogenous depression is age (Asnis, Sachar, Halbreich, Nathan, Novacenko, & Ostrow, 1981; Stokes et al., 1984). Interestingly, this association is not found in nondepressed aged individuals and appears to break down after clinical recovery in depressed patients, suggesting an age-by-illness interaction.

Virtually all studies of adrenocortical activity in depressed

patients have relied on measurement of total plasma cortisol, which is easily determined via radioimmunoassay or competitive protein-binding techniques. However, as previously mentioned, this value represents both free (active) cortisol and protein-bound (inactive) glucocorticoid, and thus is not an accurate reflector of physiologically relevant cortisol. Preliminary studies suggested that levels of plasma free cortisol are increased in depressed patients (Carroll, Curtis, & Mendels, 1976), but the interpretation of these findings is limited by the lack of appropriate normal controls, psychiatric controls, or of patient controls with other types of glucocorticoid excess. A more recent investigation (Schlecte & Coffman, 1985) of biologically active cortisol found that, as a group, depressed patients do not have significantly higher plasma free cortisol levels than do normal controls, but that dexamethasone nonsuppressors have significantly higher levels than do suppressors. However, in this study, levels in the former group were 60 per cent below those observed in patients with Cushing's disease (hyperadrenocorticism resulting from neoplasms of the anterior pituitary), and only slightly higher than those of normal controls. Measurements of plasma free cortisol collected over a 24-hour period revealed that depressed patients as a group have normal circadian variations of free cortisol, whereas patients with Cushing's disease have sustained high levels throughout the day. Finally, this study did not support an earlier conjecture (King, 1973) that unipolar depressed patients have a slightly lower cortisol binding capacity, nor was there a difference in binding capacity between dexamethasone suppressors and nonsuppressors. Although these studies suggest that

plasma free cortisol may be mildly elevated in certain subgroups of depressed patients, it is not clear whether these peripheral measures are representative of biologically active cortisol in other tissue sites such as the brain. At present, measurement of plasma free cortisol is not a clinically useful tool for the study of HPA hyperactivity in depressive illness because the assay techniques are demanding and time consuming.

More recently, there has been a renewed interest in basal levels of total plasma cortisol as a means of detecting HPA hyperactivity in depressed patients. In fact, data from Stokes and colleagues (Stokes et al., 1984) indicate that 8:00 a.m. plasma cortisol sampling has the same (albeit mediocre) diagnostic specificity, sensitivity, and predictive value for depression as the DST when used in the same patient population. Moreover, data from several recent studies (Asnis, Sachar, Halbreich, Nathan, & Halpern, 1981; Asnis et al., 1982; Stokes et al., 1984) show that cortisol hypersecretion and dexamethasone resistance are not always simultaneously present, and thus the use of both indices can describe a subgroup with perhaps the most disturbed function in depressive illness. Although elevated plasma cortisol may be a useful biologic marker in both research and clinical settings, disturbance of the HPA axis in major depression is a complex phenomenon, and single measures provide only limited insight into either the causes or the possible effects of these disturbances.

Basal plasma ACTH.

Although it has been well established that cortisol secretion is increased in many patients with acute major depression, the mechanism

of this dysregulation is still not fully understood. Carroll and Mendels (1976) have suggested that this hypersecretion of cortisol and its resistance to suppression by endogenous glucocorticoid may be secondary to a central abnormality of the HPA axis. In other words, the hypercortisolism observed in some depressed patients is secondary to pituitary ACTH hypersecretion, which itself is "driven" by execessive CRH secretion as a result of central disnhibition. Whereas this hypothesis is intuitively appealing, there have been few studies of basal ACTH levels in depression. Preliminary investigations of basal ACTH levels in depressed patients have shown elevated levels in some but not all studies (Allen, McGilvra, Kendall, Denny, & Allen, 1974; Berson & Yalow, 1968; Endo, Endo, Nishikubo, Yagamuchi, & Hatotani, 1974). These initial studies were generally uncontrolled, however, and ACTH levels were in the upper part of the normal range. Subsequent systematic studies examined plasma ACTH in depressed patients in conjunction with the overnight DST. Fang and coworkers (1981) reported no significant difference in plasma ACTH between depressed patients and controls at 8:00 a.m. before dexamethasone nor at 8:00 a.m. or 4:00 p.m. after an 11:00 p.m. oral dose of dexamethasone. Plasma cortisol levels were significantly higher in the depressed patients at all sampling times. Yerevanian and Woolf (1983) using a similar design also found no difference in ACTH levels among normal controls and depressed cortisol suppressors and nonsuppressors at either 4:00 p.m. or 11:00 p.m. despite significant differences in plasma cortisol. However, in a subsequent study by the same group (Yerevanian, Woolf, & Iker, 1983), depressed patients that were DST

nonsuppressors on admission, showed normalization of the hypercortisolism as well as concomitant reduction of ACTH levels with clinical recovery. In patients that continued to nonsuppress, ACTH remained high. Several other studies have demonstrated significant differences in ACTH between depressed DST suppressors and nonsuppressors. For example, Reus, Joseph, and Dallman (1982) reported significantly higher post-dexamethasone plasma ACTH levels in nonsuppressors at 8:00 a.m., 4:00 p.m., and 11:00 p.m.. There was also a trend for nonsuppressors to have higher ACTH levels at 8:00 a.m. pre-dexamethasone. These authors suggest that failure to suppress plasma cortisol after dexamethasone in depressed patients may be related to increased pituitary ACTH secretion. Similarly, Kalin and colleagues (1982) found elevated ACTH concentrations at 8:00 a.m. pre- and post-dexamethasone in depressed patients with HPA axis abnormality. Holsboer's group (1984), using appropriate cutoff criteria for defining cortisol and ACTH nonsuppression, reported ACTH nonsuppression in almost all of the DST nonsuppressors. Nasr and colleagues (1982), using a different assay procedure and different patient population reported no difference in ACTH levels between suppressors and nonsuppressors post-dexamethasone.

Discrepant findings in these studies may be due in part to differences in experimental design, particularly in the frequency of blood sampling. The relationship between ACTH and cortisol is complex, and owing to its relatively short half-life, single sampling may not detect a significant peak in plasma ACTH. Moreover, the cortisol level at any instant may be a reflection of the pattern of ACTH secretion

over the previous hour rather than of immediately prior ACTH concentrations. Studies employing more frequent sampling over a 24-hour period may help clarify these issues. Recently, Linkowski and colleagues (1985) described the circadian profile of plasma cortisol and ACTH in 18 depressed males and 7 age- and sex-matched controls. Although most of the cortisol bursts could be attributed to concomitant ACTH pulses in both groups, pulses were less correlated in magnitude in the depressed patients. Additionally, whereas 24 hour mean plasma cortisol levels were significantly higher in both unipolar and bipolar depressed patients than in controls, no significant difference in ACTH levels was apparent. Taken together, these findings suggest that in some depressed patients hypercortisolism may be due to increased sensitivity of the adrenal cortex to normal or only slightly elevated concentrations of ACTH. This explanation is consistent with the observations of Amsterdam et al. (1983) showing exagerated cortisol response to supra-physiological doses of ACTH, and recent reports by Gold and coworkers (1987) of blunted ACTH, but normal cortisol responses to infused CRH. Moreover, a previous multiple-sample circadian study suggests that the dissociation between ACTH and cortisol levels is even more dramatic in depressed patients who are dexamethasone nonsuppressors than in suppressors or normal controls (Sherman, Pfohl, & Winokur, 1982).

It is not surprising that these studies of simultaneous plasma cortisol and ACTH in depressed patients have found varying degrees of dissociation between the patterns of these two hormones under both basal and challenge conditions. Over the years, the adrenal cortex had

generally been viewed as responding passively to rhythmic signals from the central nervous system via the hypothalamus and pituitary, and accordingly changes in cortisol release were assumed to parallel similar changes in ACTH release by the pituitary. However, recent studies in normal humans and in animals indicate that there is not always a one-to-one correspondence between changing cortisol levels and pituitary ACTH secretion. For example, the circadian rhythm of ACTH is independent of cortisol feedback and persists even in the absence of adrenal function. Moreover, in the rat and in humans, a two-fold increase in endogenous plasma ACTH is followed by a nine-fold increment in cortisol levels (Vaughan, Becker, Allen, Goodwin, Pruitt, & Mason, 1982; Wood, Shinsako, Keil, Ramsey, & Dallman, 1982). Further, there appears to be little or no adrenal response to spontaneous spikes of biologically active ACTH during the late evening hours (Krieger & Allen, 1975). Finally, the administration of exogenous glucocorticoids may have a paradoxical effect on the hypothalamic--pituitary-adrenocortical axis in some patients with Cushing's disease (and perhaps in some depressed patients) and may actually cause an increment in plasma ACTH levels (Fehm, Voigt, Lang, Beinert, Kummer, & Pfeiffer, 1977).

If hypersecretion of cortisol in depressed patients cannot be wholly explained by corresponding changes in ACTH, then other regulatory mechanisms must be considered. Attention is now turning to other pituitary hormones such as alpha-melanocyte-stimulating hormone or beta-endorphin or vasopressin, which, under conditions of stress, may be coexpressed in the hypothalamus with CRH and hypersecreted from

the posterior pituitary. There also is evidence that glucocorticoids themselves may alter adrenal responsiveness to ACTH. One important caveat in a number of these studies is the questionable validity of some of the ACTH radioimmunoassays, since not all immunoassayable ACTH is biologically active (Krieger & Allan, 1975). Further studies are necessary to clarify whether the adrenal cortex of depressed individuals, particularly dexamethasone nonsuppressors, is more sensitive than that of healthy controls or depressed DST suppressors to circulating ACTH.

Urinary free cortisol.

Cortisol and its metabolites are excreted in the urine and can be measured as 17-hydroxycorticosteroids (17-OHCS), 17-ketogenic steroids (17-KGS), and unchanged "free" cortisol. Prior to 1970, measurements of 17-OHCS and 17-KGS were of major importance in the evaluation of HPA function in patients suffering from depression. In general, urinary excretion of these cortisol metabolites was reported to be elevated (Bryson & Martin, 1954; Bunney, Mason, Roatch, & Hamburg, 1965; Dunner, Goodwin, Gershon, Murphy, & Bunney, 1972; Kurland, 1964; Sachar, 1967). Evidence derived from clinical endocrinology, however, suggests that determination of basal levels of the urinary steroids does not always correlate well with plasma indices and may be misleading. For example, urinary 17-OHCS excretion reflects less than 50% of total cortisol secretion, and under conditions of stress may actually underestimate the degree of HPA activation (Kehlet & Binder, 1973), in part because of increasing excretion of urinary free cortisol. Likewise, the 17-ketogenic steroids may be derived from

metabolites of noncortisol steroids and thus provide only an indirect index of cortisol secretion (Cope & Black, 1959).

In spite of the fact that less than 1% of total cortisol secretion is excreted unchanged in the urine, measurement of "urinary free cortisol" (UFC) is a sensitive measure of corticosteroid production and, in recent studies, has replaced measures of 17-OHCS and 17-KGS excretion. Ferguson and colleagues (1964) were the first to note that some depressed women exhibited significantly elevated UFC excretion with a return to normal values following successful treatment with ECT. Carroll et al. (1976) and subsequently others (Anton, 1987; Nelson, Khan, & Orr, 1984; Stokes et al., 1984) reported similar findings in larger patient samples. It is noteworthy that in the Carroll et al. (1976) study, UFC levels in the Cushing's disease range were noted in 43% of depressed patient compared to only 6% of control psychiatric inpatients. Again, in most of these studies UFC levels reverted to normal with treatment and remission of the depression. Other investigators have been unable to find an increase in UFC excretion in endogenously depressed patients, although decreased levels were found with clinical improvement (Berger, Doerr, Lund, Bronisch, & von Zerssen, 1982).

Recent research by Kathol (1985) suggests that UFC excretion in some depressed patients may remain significantly elevated despite recovery from depression. Specifically, cortisol excretion in dexamethasone nonsuppressors was significantly elevated over control values, not only during a depressive episode, but also during the year following clinical recovery (particularly during the summer and fall).

These results indicate that in individuals who have recovered from depression, the circannual pattern of UFC excretion is lost. Previous studies measuring urinary 17-OHCS (Ahuja & Sharma, 1971; Watanabe, 1964) and UFC (Touitou, Sulon, Bogdam, Reinberg, Sodoyez, & Demey-Ponsart, 1983) in normal persons have identified a circannual rhythm of steroid excretion with peak values in the winter and nadirs in the summer. Most importantly, these preliminary data suggest that increased UFC may be a trait marker for major depression in patients who nonsuppress when ill. An equally compelling explanation is that chronic exposure to elevated levels of cortisol during illness may, by decreasing pituitary responsitivity to circulating cortisol, be involved in raising the set point for normal steroid production when the patient recovers.

Elevated UFC in depressed patients has been associated with a number of clinical and demographic variables. Milln, Bishop, and Coppen (1981) reported a significant increase in UFC in patients classified as endogenous on the Newcastle Scale as compared to those with "neurotic" depression [Note: The concept of "neurotic" depression is no longer meaningful, since it has not been characterized phenomenologically in a reliable way; however, many of the factor analytic studies of the '60s and '70s preferred this term because of the items which were related to it: self-pity, heterogeneity of presentation, mood responsivity, irritability, hypochondriasis, initial insomnia, sudden onset, and precipitating factors.] No significant relationship between UFC and family history of affective disorder (Winokur's (1979) classification) was noted.

Recent data presented by Anton (1987) suggest that although depression per se produces HPA disturbances, the system is more likely to be perturbed in patients with psychotic features. In this study, UFC was examined before and after administration of dexamethasone in 32 patients with major depression, 18 with psychotic features (DSM-III criteria), and 14 without psychotic features. Patients with psychotic features were more likely to have had UFC excretion greater than 90 mcg/24 hours before dexamethasone administration and greater than 20 mcg/24 hours following dexamethasone. Of note is the fact that psychotic patients who had high cortisol excretion (>90 mcg/24 hours) were older than patients who had lower and more normal cortisol excretion. In fact, all of the psychotic patients with high cortisol excretion were over 55 years of age. This data suggests an age X diagnosis interaction, such that, if a patient is greater than 55 years of age and has a depression with psychotic features, he is more likely to have abnormally elevated UFC. This data is consistent with previous reports of an association between age and baseline serum cortisol in depressed patients (Asnis, Sachar, Halbreich, Novacenko, & Ostrow, 1981; Stokes et al., 1984), and between age and dexamethasone resistance (Stokes et al., 1984). The relationship between age and excretion of UFC has also been observed in acutely stressed elderly persons (Jacobs, Mason, Kosten, Brown, & Ostfeld, 1984). Specifically, elderly persons whose spouses had been hospitalized with life-threatening illness, excreted larger amounts of UFC than did middle-age persons under the same circumstances. The magnitude of the relationship between age and UFC excretion was even greater among

spouses with high depression scores.

Similarly, a study by Dolan and coworkers (1985) revealed that depressed patients with antecedent stressful life events or difficulties had greater 24-hour UFC levels than those without, suggesting that acute stress may compound depression-related perturbations in HPA function. Of interest, is the apparent dissociation between UFC excretion and DST response in this group, since suppressor/nonsuppressor status was not associated with a greater or lesser likelihood of an antecedent life event or disturbance. This data is consistent with a recent report by the Psychobiology of Depression Collaborative Project (Stokes et al., 1984) which indicates that a finding of increased UFC excretion does not necessarily insure that an individual will nonsuppress on the DST. This finding of a dissociation between DST outcome and other measures of HPA activity suggests that different levels of HPA regulation may be involved in producing the hypercortisolism seen in depressed patients.

Of particular relevance to the present study is the recent finding that UFC levels in depressed patients correlated positively with cognitive dysfunction, and that all UFC hypersecretors were cognitively impaired on a test of concept formation (Rubinow, Post, Savard, & Gold, 1984). This finding raises the possibility that hypercortisolism produces functional changes in the brain that result in intellectual disturbances, or that cognitive dysfunction, HPA activation, and depression are all manifestations of a common underlying biologic defect. It also raises the possibility that depressed patients with hypercortisolism may manifest disturbances in other cognitive

functions, beyond those assessed by the Halstead-Reitan Category Test.

The dexamethasone suppression test

Development and diagnostic utility.

Recent developments in clinical psychoneuroendocrinology have made it clear that both basal measures and dynamic integrative measures of HPA function are needed to elucidate the mechanisms underlying the HPA activation observed in depression. One of the most widely used dynamic tests of HPA regulation in clinical psychiatry involves the attempted suppression of the system by exogenous corticosteroids such as dexamethasone (9-alpha-fluoro-16-alpha-methyl prednisolone). The dexamethasone suppression test or DST was originally developed by Liddle (1960) to assess disturbances of feedback inhibition in patients with Cushing's syndrome. In its original form, the DST involved the administration of 0.5 or 2.0 mg of dexamethasone at 6-hour intervals for 48 hours. Plasma cortisol (or 17-OHCS) and urinary 17-OHCS (or cortisol) were measured over this period. In addition, two complete 24-hour urine collections were required. This procedure is time consuming and susceptible to systematic errors (e.g., due to incomplete urine collections). Subsequently, Nichols et al. (1965) showed that the suppressive effects of dexamethasone on cortisol secretion vary greatly depending on the time of steroid administration. Temporary suppression occurred at 8 a.m. and 4 p.m., whereas the same dose given at midnight produced almost total suppression for 24 hours in normal controls. From these observations, the single dose dexamethasone test was developed, in which 1 mg of dexamethasone was

given at the critical point for CNS programming of circadian HPA activity, i.e., at 11 p.m. or midnight (McHardy-Young, Harris, Lessoff, & Lyne, 1967; Nugent, Nichols, & Tyler, 1965; Pavlatos, Smilo, & Forsham, 1965). This test is essentially the progenitor of the DST now used in psychiatric settings. Further endocrine studies with the 1 mg overnight DST indicated that the normal response (suppression) was reflected by plasma 17-OHCS levels of <5 mcg/dl (Pavlatos, Smilo, & Forsham, 1965; Tucci, Jagger, Lauler, & Thorn, 1967).

Soon after the DST was established as a reliable instrument in the differential diagnosis of Cushing's syndrome, the test was adapted for use in psychiatric populations. Although Carroll (Carroll, Martin, & Davies, 1968) has generally been considered to be the "Father of the DST" in psychiatry, two other groups actually pioneered this research in depressed patients. Gibbons and Fahy (1966) administered an intramuscular injection of dexamethasone to depressed and control subjects at 2 p.m. and measured plasma cortisol levels over the next 3 hours. No difference in post-dex cortisol levels was observed between the two groups, and the authors concluded that the acute suppressive effects of dexamethasone are not altered in depressed patients. In the same year, Stokes (1966) presented a study of dexamethasone given at midnight. A number of depressed patients showed feedback disinhibition characterized by high plasma 17-OHCS levels at 8 a.m. the following morning. These results were replicated in 1970 and a detailed report on the functions of the HPA system in psychologically disturbed (mostly depressed) individuals was issued in 1972 (Stokes, 1970, 1972). Even with doses of dexamethasone as high as 8 mg, many depressed patients

failed to normally suppress plasma 17-OHCS levels (Stokes, 1972; Stokes, Pick, Stoll, & Nunn, 1975).

During this period, a number of investigators using a variety of methodologies and criterion values for plasma cortisol suppression observed inadequate suppression with dexamethasone in about 50% of the depressives tested (Butler & Besser, 1968; Carroll, Martin, & Davies, 1968; Platman & Fieve, 1968). These findings were correlated with features of endogenous depression (Carroll & Davies, 1970), and with the physiologic symptoms of depression (Carroll, 1972). Abnormal pretreatment responses to dexamethasone were also associated with poor treatment response (McLeod, Carroll, & Davies, 1970), and failure to suppress at the time of discharge was associated with early relapse. Over the years, DST nonsuppression has been related to a number of clinical variables. These findings will be summarized later in this section.

In these early studies, plasma cortisol following dexamethasone was only sampled at 8 a.m.. Carroll, Curtis, and Mendels (1976) suggested and subsequently showed that the sensitivity of this test (i.e., true positive rate or percentage of depressed patients with nonsuppressing DST) could be increased by the addition of afternoon (4 p.m.) and evening (11 p.m.) post-dexamethasone sampling times. This modification is based on two premises: first, that normals suppress for 24 hours following dexamethasone, and second, that the HPA response to dexamethasone is not "all-or-none", but rather graded. Thus, by sampling at different time points post-steroid administration, a continuum of responses to dexamethasone, ranging from absolute

resistance to HPA suppression to early "escape" from suppression, were observed in depressed patients. Carroll et al. (1981) reported a sensitivity of about 65% in the diagnosis of endogenous depressive illness using this modification, and a specificity (true negative rate or percentage of nondepressed patients with suppressing DST) of about 95%. Based on data pooled from 200 reports on over 7500 subjects studied within the past five years, Arana and Baldessarini (1987) reported that the sensitivity of the DST in major depression is actually closer to 50%, and that the basis for this limited sensitivity is not yet known. Although there are many possible reasons for poor sensitivity in a diagnostic test, Meller et al. (1988) suggest that one or both of the following considerations may account for the limited sensitivity of the DST in depressed patients: (1) the DST is a good marker for HPA dysfunction but few patients have abnormalities in this axis; and/or (2) HPA abnormalities are quite common in major depression, but alternative neuroendocrine tests (or combinations of tests) are needed to detect HPA dysfunction. To test these hypotheses, this group administered the DST in conjunction with arginine vasopressin stimulation and insulin-induced hypoglycemia challenge to 23 depressed patients and 19 control subjects. The three separate tests identified unique subsets of patients with abnormal results, although no subject was abnormal on all three tests. Six depressed patients (26%) showed abnormal responses on two of the tests, while 13 of the patients (57%) were abnormal on at least one test. Of these 13 patients, only 6 had positive DSTs, suggesting that the low sensitivity of the DST is due, at least in part from its inability to identify a

number of patients who do have HPA abnormalities. This data also indicates that a percentage of patients with major depression may not have HPA abnormalities, but that neuroendocrine assessment at different levels of the system (adrenals, pituitary, hypothalamus) is clearly necessary to rule out different manifestations of HPA dysfunction.

In subsequent work, decreased specificity has been observed in conjunction with the increased sensitivity that multiple post-dexamethasone sampling provides (Stokes, Frazer, & Casper, 1981). Recently, a large multicenter collaborative study (Stokes et al., 1984), reported an increased incidence (35%) of DST nonsuppression in 77 normal healthy controls based on sampling at 8:30 a.m., 4 p.m., and 10 p.m. post-dexamethasone. Moreover, nonsuppression was observed in 50% (8/16) manics, and was not significantly associated with melancholia, endogenicity, or psychoticism. Other psychiatric illnesses such as anorexia nervosa and bulimia (Gerner & Gwirtsman, 1981; Hudson et al., 1983) have also been associated with an abnormal DST, and preliminary data suggest that depressed patients with borderline personality disorder have a high frequency of abnormal DSTs (Carroll et al., 1981). Additionally, Curtis, Cameron, and Nesse (1982) found a 20% incidence of abnormal DSTs in patients with agoraphobia and panic attacks. There is also a strong indication that the DST may be abnormal in schizophrenics as well. Banki, Arato, & Rihmer (1984) reported nonsuppression in 42% of patients meeting DSM-III criteria for schizophrenia, while Dewan and colleagues (Dewan, Pandurangi, Boucher, Levy, & Major, 1982) observed nonsuppression in 30% of nonmelancholic chronic schizophrenics. Nonsuppression appears

to be associated with specific subtypes of schizophrenia, particularly those which share clinical features of the afffective disorders, such as hebephrenic, acute (schizophreniform), and catatonic subgroups (Banki, Arato, & Rihmer, 1984). Patients with psychoneurologic illnesses such as temporal lobe epilepsy (Carroll et al., 1981), Alzheimers disease (Nelson, 1982; Spar & Gerner, 1982), and organic affective syndrome (Evans & Nemeroff, 1984) may show abnormal DSTs, as may those experiencing early or late withdrawal from alcohol (Ravi et al., 1984). Thus, while the specificity of the DST in diagnostic testing is about 95% if young healthy control subjects are used, differentiating this group from a group of depressed patients is rarely of interest. A more germane issue is the specificity of the DST when the test is used in patients with other psychiatric or medical disorders that might mimic the clinical signs and symptoms of major depression. In such cases, the DST has significantly lower specificity.

Finally, the positive predictive value (PPV) of the DST (i.e., the likelihood that an individual yielding abnormal test results is depressed) is only moderate. Stokes and colleagues (1984) found the PPV for an 8:30 a.m. post-dexamethasone cortisol level of $\geq$ 5.0 mcg/dl in a population consisting of 50% depressed patients and 50% healthy controls to be 75%. The PPV was not enhanced by additional blood sampling at 4 p.m. and 10 p.m., as had been suggested by Carroll et al. (1976).

What these studies suggest is that at best, the DST has very limited clinical utility as a screening test for depression.

Clinicians and researchers familiar with its shortcomings may use it as an ancillary measure to assist in treatment decisions when diagnosis is uncertain, but an affective disorder is suspected. In such instances, a positive (abnormal) result can be useful; however, a negative result is of little value. The DST may, however, have other potential uses as summarized by Rush (1983): (1) to evaluate clinical response; (2) to reflect short- or long-term prognosis; (3) to aid in selection of treatment modality; (4) to reflect underlying pathophysiology; and (5) to identify "at risk" individuals prior to clinical onset of the illness. Technical and methological limitations of the DST warrant further examination if the disputes over test validity are to be reconciled.

Sources of variation in DST results.

In the past few years, a growing body of literature has emerged which focuses on the sources of variation in DST findings across different research centers. One obvious potential source of variance is patient noncompliance with oral doses of dexamethasone. Measurement of plasma dexamethasone concentrations or addition of methylene blue to dexamethasone preparations to tint the urine (Kraus, Grof, Harvey, & Hux, 1986) are currently the best available methods to confirm compliance.

A number of concurrent medical conditions or drugs can also produce spurious DST results, as can the stress of hospital admission per se (Coccaro, Prudia, Rothpearl, & Wurnberg, 1984). Anticonvulsant and sedative hypnotic preparations such as phenytoin, carbamazepine, and phenobarbitol can interfere with DST results by inducing hepatic

enzymes that accelerate dexamethasone metabolism (Asfeldt & Buhl, 1969; Brooks, Werk, & Ackerman, 1972; Jubiz et al., 1970). Shorter-acting barbiturates (e.g., secobarbitol) may interfere with long-term dexamethasone administration, but apparently not the overnight DST (Stokes, Pick, Stoll, & Nunn, 1975). Individuals who are pregnant or taking estrogens (including oral contraceptives) have elevated total and free plasma cortisol levels, and increased UFC excretion (Burke, 1969; Burke & Roulet, 1970; Rosenthal, Slaunwhite, & Sandberg, 1969). Alphamethyldopa, meprobamate, spironolactone, high dose benzodiazepines, glucocorticoids (Brown & Shuey, 1980), cyproheptadine, and reserpine (Carroll et al., 1981) may also produce spurious results.

In addition to those psychiatric and psychoneurological conditions previously mentioned, many major physical disorders such as uncontrolled diabetes mellitus (Cameron, Kronfol, Greden, & Carroll, 1984; Hudson et al., 1984), congestive heart failure (Connolly & Wills, 1969), pulmonary, hepatic (Baxter & Tyrrell, 1987), or renal disease (Workman, Vaughan, & Stone, 1986), disseminated cancer (Brown, Johnson, & Mayfield, 1979), and dehydration or high fever (Connolly, Gore, & Stanley, 1968) may result in HPA activation before and after dexamethasone. A number of endocrine conditions such as hypo- and hyperthyroidism, hyperparathyroidism, ovarian tumors, and Cushing's syndrome can be associated with an abnormal DST (Baxter & Tyrrell, 1987). Hypopituitarism or Addison's disease will result in a false negative test. Even minor medical conditions such as the common cold or use of over-the-counter medications such as antihistamines and cold preparations can produce false-positive test results. For example,

abnormal DSTs were observed in 55% of nondepressed subjects who either had mild infections and/or were taking antibiotics, cold medications, or thyroid replacement hormones (Rush, Schlesser, & Giles, 1982). Regular alcohol consumption (Newsom & Murray, 1983) and large quantities of caffeine intake (Uhde, Bierer, & Post, 1985) can also induce escape from dexamethasone suppression. Cigarette smoking has also been found to temporarily but significantly increase adrenocortical activity (Gwirtsman, Gerner, & Sternbach, 1982), but the effects of chronic smoking on the DST are not known. These studies suggest that patients who are evaluated with the DST must be extensively screened for exclusion criteria before results can be meaningfully interpreted.

A third potential source of variability on DST outcome is the use of different assay methods (radioimmunoassay [RIA], competitive protein-binding assay [CPBA], fluorometry, high performance liquid chromatography [HPLC], and mass spectroscopy [MS]). These methods have resulted in significant discrepancies in reported plasma cortisol levels (Meltzer & Fang, 1983), particularly in the low concentration range, around 5 mcg/dl (Carroll, 1982). Some studies using RIA have reported lower plasma cortisol values than with CPBA or HPLC. For example, Farmer and Pierce (1974) reported that the RIA method for serum cortisol yielded results that were 31.9% less than those obtained by the CPBA reference method. Comparison of the two assay techniques yielded a correlation coefficient of only .74. Thijssen, Van Der Berg, and Adlercrentz (1980) compared seven methods for determination of cortisol in human plasma: HPLC, CPBA, three RIA methods, and two

fluorometric methods. The assay sensitivity at lower concentrations was poor: the mean cortisol concentration for the various groups ranged from 10.6 to 18.4 mcg/dl (measured by direct RIA), well above the critical range for the DST. Although most of the methods correlated significantly with the direct RIA, the CPBA and one of the fluorometric methods produced highly discrepant values.

Other studies have observed higher plasma cortisol values with the RIA assays than with CPBA or HPLC. Seth and Brown (1978) presented evidence that the RIA for cortisol resulted in values 25%-35% greater than those observed by HPLC, but lower than those measured by fluorometry. Caldarella, Reardon, and Canalis (1982) advocated use of the HPLC method, based on their findings of high values obtained by RIA and CPBA. They attributed these results to cross-reactivity of the antibodies to cortisol to various steroid precursors and analogs such as dexamethasone. Other studies also indicate that the CPBA reacts notably with several steroids, particularly corticosterone (Arana & Baldessarini, 1987). Lanetto, Bjorkhem, & Blomstrand (1980) reported that not only do RIA and CPBA from different manufacturers yield variable results, but a given kit may produce higher or lower values for a particular sample, depending on the cortisol concentration. Moreover, improvements made in existing kits by the same manufacturer may produce further variability in the determination of cortisol levels (Wood, Harwood, & Coppen, 1983).

Other studies have reported no significant difference between various methods of plasma cortisol determination. Meltzer and Fang (1983) compared the most widely-used method (RIA), using two different

kits, with the CPBA method. They found a highly significant relationship between the CPBA and both RIA methods (r=.965 and .947), but advocated that extreme caution must be taken before adopting the standard DST criteria of $\geq$ 5.0 mcg/dl in a particular laboratory. They further suggest that any samples within the 3.0-7.0 mcg/dl range, or any other critical range, be reassayed.

Arana and Baldessarini (1987) recently summarized data from 44 reports, using either RIA or CPBA, and found that rates of cortisol nonsuppression were similar for both methods (50.1% with the CPBA and 46.2% with the RIA), however previous data published by this group (Wilens, Arana, Baldessarini, & Cremens, 1983) indicated that the RIA values for cortisol were "consistently and significantly" lower than those obtained by CPBA.

Given that cortisol levels vary between different assays, resulting in potential differences in nonsuppression criteria, and ultimately nonsuppression rates, comparisons across centers may be confusing. These observations underline the importance of establishing independent cutoff criteria for DST nonsuppression in each laboratory, and for each method of assay.

A further source of variability in the rate of DST nonsuppresion is the time of blood sampling. Data on this topic are very limited, however, since some patients initially suppress after dexamethasone (8 a.m.), and then escape from suppression later, it seems likely that a higher percentage of nonsuppressors would be obtained with 4 p.m. and 11 p.m. sampling times. Studies of medical and healthy controls suggest that 1 mg of dexamethasone produces suppression of cortisol for

24 hours in 90% of these subjects, and that this inhibition persists for 30-36 hours (Keller-Wood & Dallman, 1984; McHardy, Young, Lessoff, & Lyne, 1967). Sherman, Pfohl, and Winokur (1984) recently reported that afternoon blood samples (11-18 hours following 1 mg dexamethasone) provided greater sensitivity, while samples collected less than 9 hours or more than 21 hours post-steroid produced only slightly lower rates. A number of recent studies comparing psychiatric populations to normals suggest that test sensitivity is fairly stable for blood samples collected from 9-24 hours post-dexamethasone (Carroll, 1982; Carroll et al., 1981; Gwirtsmen, Gerner, & Sternbach, 1982). Stokes et al. (1984), however, found that patterns of cortisol response to dexamethasone were quite variable when sampled at different time points. Besides the graded pattern of escape suggested by Carroll and colleagues (1976), some patients escaped at 8:30 a.m. and then suppressed at later times, whereas others who were 8:30 a.m. suppressors, escaped at 4 p.m. and then suppressed again at 10 p.m. Stokes suggested that these peculiar patterns may reflect sampling at "peaks and troughs of the diurnal secretory pattern", possibly resulting from transient stimuli of sufficient magnitude to temporarily break through the suppressive effects of dexamethasone. Therefore, whereas multiple sampling points increased test sensitivity, it also introduced more "nonspecific noise from within the HPA system", thus lowering diagnostic confidence. These authors suggest caution in interpreting DST outcome based on multiple post-dex samples or on samples collected later in the day.

Another potential source of variability is related to the fact

that clinical investigations of the DST have used a variety of established diagnostic criteria as the independent variable in characterizing their subject population. This issue is problematic because, to date, there is no one unified and accepted theory of depression, nor is there agreement over terminology or how to validate terminology (Greden, 1987). For example, the term "endogenous" depression is defined by some groups as limbic dysregulation, by others as suggesting a genetic or familial predisposition, and by still others as implying a lack of precipitants during the ontogeny of the illness. Others simply reject the importance of such a diagnostic distinction.

The mostly widely used diagnostic systems in DST studies include the Research Diagnostic Criteria (RDC) of Spitzer and colleagues (1977), the earlier but related criteria of Feighner et al. (1972), and DSM-III criteria for melancholia. There are several major differences in the criteria for endogenous (or melancholic) depression among these three scales. Subtle but important differences also exist between these three scales and the less frequently used Newcastle Criteria (Carney, Roth, & Garside, 1965), Klein's Endogenomorphic Criteria (1974), and the Michigan Discriminant Function Index (Feinberg & Carroll, 1982). Occasional studies have even relied on their own independent diagnostic criteria, derived from established nosologies. Recent research indicates that concordance between diagnostic entities as defined by different operational classification systems is poor (Andreasen, Reich, Scheftner, Hirschfeld, & Coryell, 1984; Phillipp & Maier, 1985). Thus, subject populations selected according to different diagnostic classifications may vary dramatically from center

to center depending on which system is used and how the criteria are applied (Carroll, 1980). When the same patients are evaluated by the same researchers using different diagnostic criteria, a very heterogeneous group of "endogenously depressed" patients emerges. In an attempt to identify the weaknesses in nomenclature that impede DST reliability, Phillipp and Maier (1985) classified depressed patients according to eight different diagnostic schedules. The positive predictive value for endogenicity (or melancholia) of DST nonsuppression ranged from 53.3% to 89.9%, depending on the rating scale used. Although universal agreement on terminology is not likely within the next few years, reliablity of the DST could be enhanced by applying only one or two accepted criteria to every patient studied, thus constructing a data base for future replications (Greden, 1987).

Many other technical, physiological, and clinical factors may be potential sources of variation in DST outcome. The effects of dexamethasone on the HPA axis, and on various feedback mechanisms is still not fully understood in normals, let alone in depressed patients (Keller-Wood & Dallman, 1984). Recently, it was found that dexamethasone levels 10 hours post-oral administration can vary several-fold in psychiatric populations (and in normals), and that levels of this exogenous steroid may covary importantly with the outcome of the DST (Holsboer, 1983; Johnson, Hunt, Kerr, & Caterson, 1984; Stokes, Lasley, Sikes, & Stoll, 1986). Other groups have also corroborated that plasma dexamethasone levels are significantly lower in nonsuppressors than in suppressors (Arana, Workman, & Baldessarini, 1984; Carr, Morris, & Gilliland, 1986). Interestingly, initial

nonsuppressors have lower plasma dexamethasone concentrations when clinically depressed than after treatment and accompanying normalization to DST suppression, indicating that this phenomenon is state-dependent (Stokes, Sikes, Stoll, & Lasley, 1987). The relative contribution of dexamethasone pharmacokinetics to DST status and the mechanisms responsible for altered metabolism in nonsuppressors remain to be elucidated.

Clinical correlates of the DST.

Based on the consistent finding of DST nonsuppression in 50% of patients with major depression, it has been suggested that HPA feedback disinhibition might be a marker for a subgroup of depressed patients with a distinct pathophysiology associated with specific clinical features (Brown & Qualls, 1981). To date, few, if any consistent findings have emerged from this body of research. Although a number of clinical, demographic, and pathophysiologic variables have been found in association with HPA dysregulation, none are unique to depression or invariably present. In this section, I will briefly summarize these efforts.

Endogenicity/Melancholia.

The DST was originally reported to be highly specific for endogenicity or melancholia (Carroll, Curtis, & Mendels, 1976; Carroll, 1978), based on non-operationalized criteria for these features (Zimmerman, Coryell, & Pfohl, 1986). Subsequent studies using more widely used and clinically-validated criteria, such as the DSM-III criteria for melancholia, or RDC criteria for endogenous subtype, do not consistently find differences in frequency of endogenous symptoms

or melancholia between DST suppressors and nonsuppressors (Berger, Doerr, Lund, Bronisch, & von Zerssen, 1982; Meltzer & Fang, 1983; Peselow & Fieve, 1982; Stokes et al., 1984).

Natural History.

A number of investigators have looked at the natural history of the individual to see if HPA dysregulation was associated with past psychiatric history. The distinction between primary and secondary affective disorder was developed to create a more homogeneous population of depressed patients for research purposes (Munro, 1966; Woodruff, Murphy, & Herjanic, 1967). Primary depression is defined as a depressive episode occurring in an individual with no prior history of any psychiatric illness other than depression. Secondary depression refers to depression occurring in an individual with antecedent illness, and in some cases, to patients having a severe concurrent medical disorder. Although this distinction has yet to be clinically validated, a number of investigators have reported lower rates of nonsuppression in secondary depression (Brown, Johnston, & Mayfield, 1979; Charles et al., 1981; Coryell, Gaffney, & Burkhardt, 1982). Clearly, such results can vary from study to study depending on the composition of the population in question because the definition of antecedent illness has not been well-defined. For example, a group comprised of a large number of patients with alcoholism or anorexia nervosa would be more likely to show a higher rate of nonsuppression than a group comprised of patients with previous adjustment or paranoid disorder.

Psychosis.

Some authors (Evans, Burnett, & Nemeroff, 1983; Schatzberg et al., 1983) have found that within depressed patients, nonsuppression appears to be more prevalent in patients with mood-congruent psychotic features (70-80%) than in those without psychosis (30-50%), whereas other have not (Coryell, Gaffney, & Burkhardt, 1982). A small serial DST study (Kraus & Remick, 1985) reported that the same patient may exhibit normal DSTs while psychotic, but fail to suppress when not psychotic. If the finding of an association between nonsuppression and psychoticism is replicated, it may help account for the moderately high rate of nonsuppression in other psychotic disorders such as schizophrenia and bipolar illness. At this point however, it is unclear whether this apparent association is due to the psychotic symptoms per se, or to the accompanying increase in overall severity of illness in the psychotic group.

Polarity.

The DST has little utility in discriminating between unipolar and bipolar depression. Although some studies have reported low nonsuppression rates for bipolar patients (Meltzer, Fang, Tricou, Robertson, & Piyaka, 1983; Papakostas, Fink, Lee, Irwin, & Johnson, 1981; Schatzberg et al., 1983); others have reported similar rates for bipolar and unipolars (Mendelwicz, Charles, & Franckson, 1982; Stokes et al., 1984). Still others have found a higher rate of nonsupression in manic-depressive patients (Asnis et al., 1982; Schlesser, Winokur, & Sherman, 1980). Many of these studies include only small numbers of bipolar patients (generally less than 10), so at this point it is difficult to draw any firm conclusions.

Severity.

One reason for the association of endogenicity and/or psychoticism with nonsuppression may be that these patient subgroups are more severly depressed, making it difficult to tease apart the relative contribution of these attributes. Carroll, Mendel, & Davies (1976) suggest that the more severely depressed patients showed cortisol escape from dexamethasone suppression earlier in the day. Several other groups (Brown, Johnston, & Mayfield, 1979; Davies et al., 1981; Holsboer, Bender, Benkert, Klein, & Schmauss, 1980) also observed a relationship between nonsuppression and severity, but did not distinguish which patients were endogenous and which were not, making it difficult to ascertain the contribution of this variable to severity. Other investigators (Aggernaes et al., 1983; Kasper & Beckmann, 1983) included only endogenous patients in their studies, and did note an association between severity and nonsuppression. Carroll's group (Carroll & Davies, 1970; Carroll et al., 1981) was unable to replicate their previous finding of an association (Carroll, Martin, & Davies, 1968), as were several other groups (Coppen et al., 1983; Giles & Rush, 1982; Targum, Rosen, & Capodanno, 1983). However, data presented from serial DSTs conducted within patients during the course of a depressive episode, reveal a relationship between post-dexamethasone cortisol levels and severity using the Hamilton Depression Rating Scale (Holsboer, Liebl, & Hofschuster, 1982; Greden et al., 1983). Also, it appears that if severity is used as the independent variable, and patients are ranked by Hamilton scores and then stratified into categories ranging from least to most severe,

nonsuppression rates increase in a stepwise fashion (Brown, 1987). Indicators of severity other than total number and intensity of symptoms may also be associated with the probability of nonsuppression. For example, nonsuppressors may spend a longer time in the hospital than suppressors (Brown, 1987), and are less likely to recover with placebo treatment than suppressors (Shrivastava, Schwimmer, Brown, & Arato, 1985). All of the aforementioned studies have relied on objective, investigator-administered rating scales with heavy loading for the quantitative or vegetative aspects of depression to assess severity of depression. Few studies have included self-rating scales such as the Beck Depression Inventory or the Raskin Mood Scale to assess severity in relation to HPA hyperfunction. Greater subjective distress in DST nonsuppressors is suggested by a recent preliminary study of depressed inpatients showing that nonsuppressors perceive themselves as being significantly more depressed, anxious, fatigued, and cognitively impaired than suppressors (Sikes & Stokes, 1987). Taken together, these studies lend support to the growing consensus that a number of measures of severity, confounded as they may be by other variables, appear to be linked to HPA disinhibition.

Family history.

The relationship between HPA dysregulation and family history remains obscured because Winokur's (1971; 1978) typology has yet to be validated. Winokur proposed that depressed patients could be subtyped into 1 of 3 groups based on the presence or absence of psychiatric history in the family of the proband: familial pure depressive disease or FPDD -- patients who have a family history of any depression);

depression spectrum disease or DSD (patients with a family history of antisocial personality, alcoholism, hysteria, or drug abuse, either alone or in combination with depression); and sporadic depressive disorder or SDD (patients with no family history of any major psychiatric disorder as defined by the Research Diagnostic Criteria). Recent studies of this classification system using the DST have reported a higher nonsuppression rate in FPDD subtype (Schlesser, Winokur, & Sherman, 1980; Targum, Byrnes, & Sullivan, 1982; Coryell et al., 1983), although there are discrepant findings on the rate of nonsuppression in the DSD and SDD subtypes. Other studies have found no difference between the subtypes, possibly due to the small number of patients in each subgroup (Asnis et al., 1982; Carroll et al., 1980; Kasper & Beckmann, 1983), while Rudorfer and colleagues (1982) found the greatest rate of nonsuppression in the SDD group. Thus, while the association between family history and DST status is an intriguing prospect, this relationship has not been sufficiently replicated, particularly outside the center where it was originally proposed.

Suicide.

Recently, a number of perspective studies have suggested an association in depressed patients between nonsuppression and suicide (Greden et al., 1980; Papakostos, Fink, Lee, Irwin, & Johnson, 1981; Yerevanian et al., 1983). In fact, if the data from these 3 studies are combined, 5 of 18 non-normalizers eventually committed suicide, while there were no suicides among the normalizers. Carroll, Greden, & Feinberg (1981) report that of 5 depressed patients who suicided and 11 who made serious attempts, all had been nonsuppressors. Targum and

colleagues (1983) found that 14 of 17 endogenously depressed patients who had made a suicide attempt were nonsuppressors, compared with 9 of 32 nonsuicidal depressed patients. The patients who suicided, however, were severely depressed, and as previously discussed, this may be a factor in determining nonsuppression. Results from these studies of suicide and DST status are difficult to interpret for a number of reasons. First, because nonsuppression and suicide are both correlated with severity of depression, both will tend to occur together so that nonsuppression may not actually be a predictor of suicide. Second, it is often difficult to interpret the results of a retrospective study, especially when measures of HPA function may have been made at time points ranging from months before to days after a suicide attempt. Third, suicide is a complex multidetermined phenomena co-occurring with a variety of psychological conditions including absence of prominent psychopathology. Therefore, one would not necessarily expect a single unique, biological substrate.

Treatment response.

Although the notion that DST nonsuppressors show a better treatment response to biological interventions such as tricyclic antidepressants (TCAs) is intuitively appealing, this suggestion has not consistently held up under empirical testing. To date, the studies examining this issue have been equally divided between those which report no difference between suppressors and nonsuppressors (Amsterdam, Bryant, Larkin, & Rickels, 1983; Extein, Kirstein, Pottash, & Gold, 1982-3; Green & Kane, 1983; Peselow & Fieve, 1982), and those which show that abnormal DST results may be predictive of a better reponse to

somatic treatment (Ames, Burrows, Davies, Maguire, & Norman, 1984; Brown, Johnston, & Mayfield, 1979; Brown & Qualls, 1981; Brown & Shuey, 1980; Greden et al., 1981; Klein, Bender, Mayr, Niederschweiberer, & Schmauss, 1984). Other authors report no significant difference in overall therapeutic improvement between pretreatment suppressors and nonsuppressors, but a significant correlation between admission post-dexamethasone cortisol levels and greater clinical improvement (Coppen, Milln, Harwood, & Wood, 1985; Nelson, Orr, Stevenson, & Shane, 1982). Closer scrutiny of these studies reveals that 3 of 5 of those concluding that DST results do not predict treatment response involved primarily outpatients (Amsterdam, Bryant, Larkin, & Rickels,1983; Green & Kane, 1983; Peselow & Fieve, 1982), whereas all of those studies finding a positive association used only inpatients. Differences in severity of illness and greater placebo response in the outpatient group may account for some of the discrepant findings between the two populations. Finally, two studies conducted at the Royal Melbourne Hospital (McLeod, Carroll, & Davies, 1970; McIntyre, Norman, Burrows, Davies, & Maguire, 1981) reported that the majority of nonsuppressors failed to respond to TCAs, while most of the suppressors did respond. These results have not been replicated outside this center, and a subsequent report by the same group (Ames, Burrows, Davies, Maguire, & Norman, 1984) did not support the previously noted findings of a relationship between DST nonsuppression and poor response to TCAs.

One finding which does appear to be well-supported is the data that indicate that as patients with depressive illness recover, so does the HPA axis (Brown & Shuey, 1980; Carroll, Curtis, & Mendels, 1976).

Conversely, those who do not improve, show continued nonsuppression (Brown & Shuey, 1980; Carroll, Curtis, & Mendels, 1976). In patients who have been nonsuppressors during a particular episode, and have then recovered, relapse is often anteceded by a shift back to nonsuppression (Brown & Qualls, 1981; Rothschild & Schatzberg, 1982). The small group of depressed patients who continue to nonsuppress despite apparent clinical improvement have been found to have a relatively poor prognosis characterized by relapse, suicide attempts, or persistent symptomatology during the months following hospitalization (Greden et al., 1981; Nemeroff & Evans, 1984). At this point in time, the association between poor prognosis and continued HPA disinhibition appears to be one of the most promising clinical correlates of the DST.

Age.

A relationship between age and pituitary-adrenocortical dysregulation in depressed patients has been fairly consistently observed in the literature. A number of studies have shown that older (>55 years of age) depressed patients are more likely than younger patients to show cortisol resistance to dexamethasone (Alexopoulus et al., 1984; Asnis et al., 1981; Davis et al., 1984; Kocsis, Brockner, Butler, Fanelli, & Stokes, 1982), and that among depressed patients, post-dexamethasone plasma cortisol is significantly correlated with age (Stokes et al., 1984). This finding is notable because the HPA response to the dynamic tests most commonly used has been thought to be relatively resistant to the effects of aging. For example, the rise in plasma cortisol level in response to insulin hypoglycemia and the increase in plasma total corticosteroids to IV metyrapone in senescent

individuals is indistinguishable from the adrenocortical response observed in younger subjects (Blichert-Toft, 1975; Cartlidge, Black, Hall, & Hall, 1970). Advanced age also does not appear to significantly alter the circadian pattern of cortisol secretion or basal levels of plasma cortisol (Dean & Felton, 1979; Grad, Rosenberg, & Liberman, 1971). Studies using ACTH stimulation have also seemed to indicate unimpaired adrenocortical responsiveness while using plasma cortisol levels as the dependent measure (West et al., 1961), but diminished responsiveness when judged by the urinary 17-OHCS excretion (Monocloa, Gomez, & Pretell, 1963). This latter finding is related to the fact that secretion and urinary excretion of cortisol may diminish with age, largely reflecting reduced adrenal contribution (Grad, Rosenberg, & Liberman, 1971). The finding of decreased cortisol secretion in old age, but unaltered basal levels of plasma suggests that cortisol production is adjusted to the slowed metabolic disposal by normal feedback mechanisms. The supposition of normal feedback control in senescense is further supported by the detection of unchanged levels of urinary free cortisol with age (Blichert-Toft, 1975). However, several recent studies in rats and both healthy subjects and nondepressed psychiatric patients revealed a clear association between age and resistence to dexamethasone suppression (Oxenkrug et al., 1983; Oxenkrug, McIntyre, Stanley, & Gershon, 1984; Riegle & Hess, 1972; Sapolsky, Krey, & McEwen, 1983). Closer inspection of the age/HPA function relationship in depressed patients also suggests that the increased propensity to feedback disinhibition seems to occur after age 55-60 (Davis et al., 1984), and until that

age, nonsuppression rates do not consistently covary with age (Davis et al., 1984; Kocsis, Brockner, Butler, Fanelli, & Stokes, 1984). At this point, the basis for the relationship between DST nonsuppression and aging is not readily apparent. Although it is possible that this decreased resistance to dexamethasone suppression is related to altered dexamethasone pharmacokinetics, this seems unlikely since the diminished liver microsomal enzyme activity associated with aging would tend to result in higher plasma concentrations of dexamethasone, and thus lower post-dexamethasone cortisol levels in older compared to younger subjects. This phenomena may also be due in part to age-related changes in the metabolism of biogenic amines which modulate HPA function, such as epinephrine or norepinephrine (McGeer & McGeer, 1976; Moore, 1979). Finally, recent data from rat studies (Sapolsky, Krey, & McEwen, 1986), suggest there may also be an age-dependent shift in the HPA system's sensitivity to feedback disinhibition due to glucocorticoid receptor depletion in the hippocampus and amygdala, areas which exert an inhibitory influence over adrenocortical activity. This depletion of brain target cells appears to be due, at least in part, to the "gradual and prolonged catabolic actions" of even normal levels of circulating hormones over time (Landfield, Waymire, & Lynch, 1978), thus resulting in a "runaway positive feedback loop" between the CNS and the endocrine gland (Landfield, Waymire, & Lynch, 1978). Thus, while aging per se may cause diminished sensitivity to the suppressive effects of dexamethasone, depression and aging appear to act synergistically to result in an even greater propensity to escape from dexamethasone suppression.

Weight Loss.

Several lines of evidence suggest an apparent association between DST nonsuppression and weight loss in populations other than depressed patients. Weight loss in anorexic patients and in patients with severe protein/caloric restriction is correlated with DST nonsuppression (Doerr, Fichter, Pirke, & Lund, 1980; Smith, Bledsoe, & Chhetri, 1975). Acute weight loss due to caloric restriction in normals (with no change in affect) has been found to produce a switch to nonsuppression (Berger, Pirke, Doerr, Krieg, & von Zerssen, 1983; Edelstein, Roy-Byrne, Fawzy, & Dornfield, 1983). Morevoer, starving normal controls who nonsuppress when deprived, revert to suppression rapidly after starting to eat (Berger, Pirke, Krieg, & von Zerssen, 1985). As weight loss often accompanies depressive illness, a number of investigators have questioned whether DST nonsuppression in some patients is actually an epiphenomenon, thus rendering such DST results ambiguous. The reports so far are evenly split between those which have noted no relationship between DST nonsuppression rates and weight loss (Coppen, Harwood, & Wood, 1984; Krishnan, France, Snipes, & Pelton, 1985; Yerevanian, Baciewicz, Iker, & Privitera, 1984), and those which have (Berger, Prike, Krieg, & von Zerssen, 1985; Holsboer, Doerr, & Gerkin, 1984; Kline & Bieber, 1983; Targum, 1983). These findings are difficult to reconcile in light of varying selection criteria (e.g., some studies excluded patients who had lost >20 lbs.), overall sample differences, lack of control for the effect of other intervening variables, and the use of "reported" vs. "measured" weight loss as the independent variable. What does emerge from these studies is that an

abnormal DST is correlated with acute weight loss in some depressed patients, but not in others. Moreover, nonsuppression can persist despite a return to normal diet and nutritional status (Targum, 1983). This is in marked contrast to the DST studies in dieting in starving control individuals (Berger, Pirke, Doerr, Krieg, & von Zerssen, 1983; Edelstein, Roy-Byrne, Fawzy, & Dornfield, 1983), suggesting that CNS control of appetite and satiety may differ substantially in these two conditions, and may result in different patterns of endocrine disturbance (Morley & Levine, 1983). Additionally, it is difficult to tease apart the relative contribution of weight loss per se, vs. the catabolic state, vs. caloric or protein/carbohydrate restriction in each of these studies. Indeed, it may be that acute rapid weight loss acts as a psychophysiological stress for which cortisol nonsuppression is a relatively nonspecific marker, and that moderate weight loss over a prolonged period does not significantly affect DST outcome. At this point, it is safe to conclude that DST nonsuppression is probably not an artefact of weight loss in most depressed patients, but weight change should be carefully noted and perhaps controlled in evaluating positive DST results.

Depressive symptoms.

Although single studies have reported differences between suppressors and nonsuppressors in the frequency or intensity of various depressive symptoms (Brown & Qualls, 1981; Kocsis et al., 1985; Reus, 1982), these studies are sporadic, and there have been no consistently demonstrated clinical/behavioral symptoms associated with hyperactive HPA function. Various studies have, at one time or another, reported

that DST nonsuppression in depressed patients is significantly correlated with symptoms of anxiety and agitation (Kasper & Beckmann, 1983; Kocsis et al., 1985; Zimmerman, Coryell, & Pfohl, 1986), sleep disturbance (Kocsis et al., 1985; Miller & Nelson, 1987; Reus, 1982), diminished sexual interest (Miller & Nelson, 1987), hypochondriasis (Klein, Bender, Mayr, Niederschweiberer, & Schmauss, 1984), obsessive-compulsiveness (Nasr et al., 1983), and loss of insight (Nasr et al., 1983). Other studies found a significant association between DST suppression and various clinical symptoms, including diurnal variation (Brown & Shuey, 1980), hypochondriasis (Nasr et al., 1983), weight loss (Nasr et al., 1983), depersonalization (Nasr et al., 1983), and cognitive impairment (Silberman, Weingartner, Targum, & Byrnes, 1985). Still others have observed that DST outcome does not actually distinguish particular signs and symptoms of depression (Brown, Johnston, & Mayfield, 1979; Calloway, Dolan, Fonagy, DeSouza, & Wakeling, 1984). These conflicting results are difficult to interpret due to relatively small samples, and use of a single rating scale and only one measure of HPA function. They do however raise doubts about the validity of using the DST as a diagnostic marker for a specific depressive syndrome.

Although an association between DST nonsuppression and specific symptoms has failed to emerge, it does appear that the symptoms that generally do correlate with a positive DST are among the vegetative or quantitative symptoms of depression. Symptoms that are mainly psychological or qualitative in nature (guilt, loss of self-esteem, suicidal ideation, helplessness, hopelessness, etc.) are rarely or

never associated with DST abnormality (Miller & Nelson, 1987).

One variable which has received little attention with regard to pituitary-adrenocortical disturbance in depression is cognitive function. Preliminary studies investigating this relationship will be discussed in the following section, as will the rationale for hypothesizing such an association.

Pituitary-adrenal disinhibition and cognitive functioning

Studies conducted on various patient groups with HPA disturbances (e.g., depressed patients, individuals with Cushing's syndrome, anorexia nervosa patients), and data derived from administration of exogenous glucocorticoids and ACTH to animals and humans suggest that elevated serum levels of HPA hormones may be accompanied by measurable CNS and and cognitive disturbances. This evidence, outlined below, serves as the rationale for the present study.

Depressed patients.

Impairment in the cognitive performance of depressed DST nonsuppressors was first inferred by Brown and Qualls (1981), based on the inability of these patients to complete self-rating scales (Zung Self-Rating Depression Scale; Profile of Mood States; Beck Depression Inventory), and relatively slowed performance on a key-pressing task. Targum, Rosenthal, and Sullivan (1983) subsequently argued that the increased incidence of suicide in DST nonsuppressors may reflect a neurobiological dysfunction which impairs both cognition and impulse control.

The relationship between cortisol dysregulation and cognitive dysfunction has been directly assessed only recently, though results are still far from conclusive. Beckwith (1977), reporting on a mixed psychiatric population, found that individuals resisting dexamethasone suppression performed significantly better on a subproblem of a concept formation task. He concluded that enhanced performance on this task reflected increased attention due to elevated levels of endogenous ACTH (although ACTH concentrations were not actually measured), similar to the performance previously observed following exogenous MSH/ACTH administration to rats and humans (Sandman, George, McCanne, Nolan, Kaswan, & Kastin, 1977; Sandman, George, Nolan, Van Riezen, & Kastin, 1975). Using measures of verbal learning and memory, Silberman, Weingartner, Targum, & Byrnes (1985) found both quantitative and qualitative differences between the performance of depressed DST suppressors and nonsuppressors. The suppressor group showed significantly poorer memory performance on a free recall and recognition task, and shallower semantic processing of stimuli (an index of emotional discrimination). These findings of cognitive impairments in depressed DST suppressors but not nonsuppressors are difficult to interpret, and generalizability may be limited for a number of reasons including: (1) small sample size; (2) lack of control for the severity of depressive symptomatology present in the two groups; and (3) the fact that depressed patients showed only minor cognitive deficits compared to controls.

Other recent studies have suggested that depressed patients with HPA abnormalities perform more poorly on selected neuropsychological

tests. For example, a relative inability to discriminate salient from irrelevant stimuli during recall was observed in depressed patients who nonsuppressed, as compared with normal controls and DST suppressors (Reus, Joseph, & Stebbins, 1982). Another group (Rubinow, Post, Savard, & Gold, 1984) observed an association between total number of errors on the Halstead-Reitan Categories Test and HPA activation (as measured by 24 hour urinary free cortisol excretion) in depressed patients. This relationship was not evident in a control population, suggesting that cortisol hypersecretion may render depressed patients more distractable. The number of test errors was not significantly correlated with ratings of depressive symptomatology, but a robust correlation between age and errors was noted in the patient group. In fact, age accounted for a greater percentage of the variance of test errors than hypercortisolism in the depressed group. This suggests that age and depression may interact to produce neuropsychological disabilities. More recently, Winokur, Black, and Nasrallah (1987) observed a relationship between nonsuppression and memory deficits assessed by a mental status examination. These deficits were unrelated to organicity or disorientation in the patients.

Finally, Caine, Yerevanian, and Bamford (1984) noted no difference between suppressors and nonsuppressors on an extensive neuropsychological battery. However, this battery contained numerous tests designed to screen for aphasia, apraxia, and other gross neurological impairments, functions which are not typically impaired in depressed patients.

At this point it is difficult to reconcile the findings of these

various studies. Disparate findings may be attributable to differences in subject pools (type and degree of depression), or to differences in cognitive functions assessed (e.g., verbal performance vs. visual-spatial skills). In addition, interpretation and generalizability of these results are limited by (1) poor experimental control (subjects were not matched for critical variables of age, IQ, and educational background); (2) restricted sample size; (3) use of only a single measure of HPA function; (4) no statistical control for number of comparisons; and (5) differences in the neuropsychological instruments employed. With regard to the latter, methods of assessing cognitive performance have ranged from subjective clinical impressions or ratings of concentration to standardized neuropsychological tests. Because these studies have relied on such diverse methodologies, and because age appears to be a confounding variable, these findings, although heuristically significant, should be considered tentative.

Recently, Sikes and Stokes (1987) studied 25 depressed inpatients using both investigator-rated and patient-rated mood scales, and an extensive battery of neuropsychological tests in conjunction with several indices of HPA function (24 hour UFC, basal cortisol and ACTH levels, 1 mg overnight DST). Suppressors (N=13) and nonsuppressors (N=12) were equivalent on variables of age, IQ, education, and observer-rated clinical severity. Preliminary results indicate that DST nonsuppressors performed significantly worse on tests of verbal learning, visual organization, and complex motor performance, with a trend towards impaired abstracting ability. Additionally, an impairment index (reflecting the total number of scores falling

significantly below test norms) was computed for each subject. A stepwise multiple regression revealed that age and a.m. post-dexamethasone cortisol each contributed significantly to the prediction of number of impairments, and together accounted for 60% of the variance in the impairment index. Furthermore, nonsuppressors showed significantly more test impairments than suppressors, even with the effects of age covaried out. This preliminary study has been extended to form the basis for the present dissertation project. If the association between HPA feedback disturbance and cognitive impairment continues to hold up in a larger sample of depressed patients, I will address the issue of whether these impairments are related to increased plasma levels of ACTH or cortisol (or perhaps both), or whether these deficits are instead intrinsic to a particular clinically or demographically distinct subgroup of depressed patients.

There is much reason to suspect that limbic structures, particularly the hippocampus, may mediate the cognitive effects of elevated levels of biologically-active cortisol. Recent neurobiological studies suggest that the hippocampus, due to its abundance of corticosteroid receptors, is subject to an unusual degree of physiological modulation by circulating glucocorticoids (McEwen, 1982). Not only can the expression of corticosteroid receptors by the hippocampus be suppressed by stress-induced elevation of circulating corticosteroids (Sapolsky, Krey, & McEwen, 1984), but vulnerability of hippocampal neurons to various metabolic insults is increased when circulating corticosteroid levels are high. This situation has profound pathophysiological consequences, ultimately producing

accelerated cell death of corticosteroid-sensitive cells (Sapolski, 1985). Since these same steroid-sensitive hippocampal cells are thought to be involved in terminating the HPA response to stress (Sapolsky, Krey, & McEwen, 1984), their absence (or diminished responsiveness to corticosteroids) could conceivably lead to a self-accelerating process of hypercortisolism and neuronal death ("glucocorticoid cascade"). At some point, such a process would express itself as a functional deficit.

Thus, there are mechanistic reasons to predict that depressed patients with chronic hypercortisolism may have a specific form of organic brain impairment, perhaps ultimately expressed as loss of specific cells. The hippocampal cells thought to be most vulnerable are critically implicated in various stages of the learning process and memory formation (Solomon, 1980; Weiskrantz, 1976). Thus it is not surprising, but rather confirmative of previous work in the neurosciences, that depressed patients with HPA hyperactivity show specific deficits (vide supra).

An additional potential link between HPA disinhibition and cognitive impairment in depressed patients is suggested by reports of computed tomography (CT scan) and electroencephalogram (EEG) abnormalities in cortisol hypersecretors. Kellner and colleagues (1983) reported a significant association between ventricular enlargement (as measured by the lateral ventricle to brain ratio or VBR) on CT scans and urinary free cortisol levels in a group of 10 afffectively ill patients. Schlegel and Krtezschmar (1987), examining a larger sample (N=60) of depressed patients, found no difference in

VBR values between DST nonsuppressors and suppressors, but did report linearly-measured ventricular enlargement of the frontal horns and the third ventricle in nonsuppressors compared to age- and sex-matched controls and depressed patients with normal DSTs. All linear ventricular values, however, were within normal known limits. This finding implies that HPA dysregulation in depressed patients is associated with more focal rather than global atrophy, in contrast to Kellner et al. (1983).

The functional significance of increased ventricular size has been investigated in schizophrenia patients. Recent work by Golden et al. (1980), and subsequently by Keilp and colleagues (1988), has demonstrated that cognitive impairment is correlated with cerebral ventricular size. These studies in schizophrenia do not address the issue of hypercortisolism as a possible explanation for this finding; however, the patient with the greatest VBR in the Keilp et al. (1988) study also had pathologically high basal cortisol levels and was a DST nonsuppressor (personal communication). Previous findings of elevated urinary 17-OHCS (Sachar, Mason, Kolmer, & Artiss, 1963) and a high incidence of DST nonsuppression in chronic schizophrenic patients (Dewan, Pandurangi, Boucher, Levy, & Mayer, 1982) support this possibility.

While it is tempting to speculate that hypercortisolism directly causes the ventricular enlargement seen in certain depressed patients, it is also possible that increased cortisol secretion is the result, not the cause, of the brain alteration observed in CT studies. This seems less likely in light of reports of exogenous glucocorticoid

administration causing ventricular enlargement in other patient populations (e.g., Bentson, Reza, Winter, & Wilson, 1978). The mechanism by which corticosteroids may produce these structural abnormalities remains largely speculative.

Electrophysiological measures of brain function also suggest an apparent relationship between cortisol dysregulation and CNS disturbance. In a retrospective study, Miller and Nelson (1987) observed that depressed patients having EEG abnormalities were more likely to be DST nonsuppressors than patients with normal EEGs, and conversely, that the probability of escaping from dexamethasone suppression increased with more severe EEG abnormality. The EEG finding most commonly noted was diffuse slowing, and in general, abnormalities were mild. Neither endogenicity nor melancholia had any effect on the EEG-DST association when entered into a regression equation, suggesting that this relationship is independent of certain diagnostic subtypes. These findings raise the possibility that increased cortisol levels may potentially produce cognitive impairment by disrupting electrical activity in the brain. In fact, exogenous administration of ACTH and corticosteroids has been found to disrupt normal EEG activity, albeit in higher doses than those typically seen in depressed patients (Gibbs & Gibbs, 1964). It is also possible that an organic brain disturbance could account for both the HPA dysregulation and the EEG abnormalities, since an association between organicity and/or dementia and DST nonsuppression has been reported by many groups (Evans & Nemeroff, 1984; Spar & Gerner, 1982). A third possibility is that EEG disturbances are related to major depression

per se, and that cortisol dysregulation and EEG abnormalities co-occur in such patients. There is some evidence to suggest that subtle EEG changes may distinguish depressed patients from other psychiatric groups and normals (Shagass, Roemer, Straumanis, & Josiassen, 1984; Snyder & Pitts, 1984).

Additional evidence for a link between cortisol hypersecretion and cognitive impairment is derived from studies of patients with endogenous hypercortisolism or Cushing's syndrome.

Cushing's syndrome patients.

The term "Cushing's syndrome" (CS) is used to denote a condition characterized by sustained hypersecretion of adrenocortical steroids (principally cortisol), due to either excessive ACTH secretion by the pituitary or some ectopic site, or to primary adrenal pathology. There are many striking qualitative similarities between the HPA disturbances of Cushing's syndrome and severe depressive illness, including elevated plasma cortisol, increased rate of cortisol production, a flattened or phase-advanced circadian rhythm, defective feedback inhibition, blunted cortisol response to hypoglycemic stress, and in some cases, elevation of ACTH (Kendall, 1984). These shared neuroendocrine abnormalities may reflect a common disturbance of central neurotransmitter systems as the pathogenetic basis for both disorders. In addition, affective disturbances (predominantly depressive) are observed in 60-75% of all patients with CS (Haskett, 1985; Spillane, 1951; Starkman, Schteingart, & Schork, 1981; Whybrow & Hurwitz, 1976). However, these estimates are plagued by a number of shortcomings. First, many of the reports were anecdotal and assessments were not performed by trained clinicians.

Second, it is often difficult to differentiate the short-lived sense of despair, hopelessness, and helplessness seen in patients suffering from a chronic illness, from the marked despondency observed in major affective illness (i.e., coping vs. the biological disturbances of depressive illness [Vaillant, 1977]). Third, many of the somatic or vegetative symptoms attributed to depression (e.g., sleep and appetite disturbances, weight loss, fatigue, diminished libido, retardation, and somatic preoccupations) are also core symptoms of most severe medical and surgical conditions. Thus, it is often impossible to ascertain whether the type or severity of depression or the severity of the medical illness is being measured (Kathol & Petty, 1981).

While there is a vast anecdotal literature describing the emotional disturbances associated with CS, only recently have systematic studies of cognitive function been conducted in this population. From a neurological perspective, the finding of gross cerebral abnormalities in a number of CS patients would suggest associated cognitive loss. For example, Momose, Kjellberg, and Kliman (1971) observed cerebral cortical atrophy in 90 per cent of a selected sample of 31 CS patients, and cerebellar changes in 74 per cent of this group. Soffer, Iannacone, and Gabrilove (1961) examined the brains of eight patients from a sample of 55 with CS. Internal hydrocephalus was found in five patients and cortical atrophy in the other three. Brain weight was below normal in these patients, and post-mortem microscopic examination revealed increased perivascular spaces. EEG abnormalities, similar to those noted in DST nonsuppressors, have been detected in patients with CS (Tucker, Weinstein, Schteingart, & Starkman, 1978).

These alterations were generally minor, consisting of diffuse slowing and disruption of background activity, excessive fast activity, and some paroxysmal changes with small spike-waves and sharp waves. The incidence and extent of these abnormalities was greater with increased serum cortisol levels. These studies suggest that if neuropsychological deficits do exist, then the pattern of deficits in some CS patients may resemble that seen in other types of diffuse bilateral neuropathy.

To date, only one group has assessed neuropsychological status in CS patients. In an initial report (Whelan, Schteingart, Starkman, & Smith, 1980), 35 patients with CS were studied prior to treatment, using the Michigan Neuropsychological Battery. Thirteen patients exhibited borderline or no signs of cognitive impairment. Ten other patients had mild deficits, eight had moderate and more frequent signs of impairment, and four had frequent and marked deficits. Thus, two-thirds of this sample showed varying degrees of cognitive loss. Although no cognitive functions were spared, impairment was more frequent and more profound in non-verbal, visual-ideational, visual memory, and spatial-constructional abilities than in language and verbal reasoning.

In a subsequent report (Starkman & Schteingart, 1981), neuropsychological disability was related to plasma ACTH and cortisol levels present in the same group of 35 patients. Overall trends suggested that cognitive disturbances (e.g., decreased concentration, inattention, distractability, impaired reasoning, disrupted memory) were associated with a high cortisol/ACTH ratio (CS due to adrenal

adenoma), while depressed mood was associated with a higher ACTH/cortisol ratio (pituitary ACTH-dependent hyperactivity). Of interest, was the lack of correlation between the patients' subjective report of concentration, thinking, and memory difficulties and actual neuropsychological performance (Starkman, Schteingart, & Schork, 1986). This may stem from the patients' own lack of awareness of the extent of cognitive slowing. The investigators' reports of cognitive impairment based on recall of three cities and serial 7's on the Mental Status Exam, provided good estimates of the actual impairment assessed by a complete neuropsychological battery.

At present it is difficult to ascertain whether intellectual disabilities are specifically related to hormonal imbalance or to other metabolic or clinical aspects of the disease. Moreover, it is not known whether cognitive status normalizes following surgical intervention to correct the disorder, nor whether cognitive improvement follows the same course of normalization as ACTH and cortisol (6-8 months). A longitudinal investigation of these issues is currently underway in our laboratory.

Anorexia nervosa (AN) patients.

A substantial body of evidence has emerged indicating that many individuals with AN manifest HPA disturbances resembling those observed in patients with CS or major depression. These abnormalities include elevated UFC and 17-OHCS (Walsh et al., 1978), elevated plasma cortisol (Casper, Chatterton, & Davis, 1979), loss of diurnal rhythm (Frankel & Jenkens, 1979), blunted cortisol response to insulin-induced hypoglycemia (Tolis, Richardson, & Crispin, 1982), and failure to

suppress cortisol following dexamethasone (Doerr, Fichter, Pirke, & Lund, 1980). Malnutrition appears to be the major determinant of these adrenocortical abnormalities; however, major depression is a common finding in AN patients, and a primary affective diathesis has been suggested on the basis of genetic studies (Winokur, March, & Mendels, 1980). In light of the parallel endocrine and mood disturbances demonstrated in CS, depressed, and AN patients, it is not surprising that the AN patients also display brain and neuropsychological abnormalities. For example, EEG abnormalities characterized by diffuse slowing, and in some cases, suggestive of paroxysmal activity have been observed in a number of AN patients (Crisp, Fenton, & Scotton, 1968). Brain CT scans on AN patients have shown ventricular dilation and sulcal prominence, earmarks of cerebral atrophy (Heinz, Martinez, & Haenggeli, 1977). Individuals with AN also display specific deviations in cognitive performance. For example, Fox (1981-82) found AN patients to be impaired on arithmetic tasks (relative to verbal skills), ability to copy complex geometric designs, and on tasks that assess attention and concentration. These visual-spatial deficits are suggestive of compromise in right hemisphere function. Witt and colleagues (1985) noted deficits in associative learning ability in AN patients compared to depressed and diabetic controls, but no differences on tasks designed to measure visual memory and rapid set alteration. Overall deficits were independent of acute weight loss at the time of testing, but were significantly correlated with duration of illness. This finding suggests that learning deficits may be related to the profound endocrine and metabolic disturbances that accompany prolonged periods

of starvation and vitamin deficiency. Hamsher, Halmi, and Benton (1981) administered a neuropsychological battery covering a broad array of cognitive functions to 20 AN patients at the beginning of hospitalization and again following treatment (when at normal weights). On pretreatment evaluation, 14 of the patients (70%) showed impairment on at least one measure. Following treatment, 12 patients (60%) continued to exhibit impaired performance on at least one test. The nature of these disturbances was generally nonspecific, however a number of patients did show impairments in complex reaction time and/or shortterm visual-spatial memory.

Although it may be hypothesized that the cognitive dysfunction in AN patients is brought about by endocrine (possibly HPA) concomitants of the disease, any attempt at explanation is confounded by a variety of physiological, psychological, and behavioral abnormalities that co-exist with the disorder, especially in those with protracted symptoms and chronic inanition.

Effects of ACTH and corticosteroids on cognitive functioning.

An increasing body of evidence has indicated that HPA axis hormones are involved in modulating cognitive performance. Most of the current research has focussed on the influence of exogenously administered ACTH or corticosteroids on learning and retention in intact animals or humans. Earlier studies in rats examined the effects of hypophysectomy and adrenalectomy on the acquisition of avoidance responses. The theoretical basis for these studies is derived from Woodbury's (1954) research which provided evidence that cortisol and ACTH alter brain excitability. This section will provide a brief

review of studies performed during the last 25 years.

Because corticosteroids are released in response to aversive stimuli, their influence on conditioned avoidance behavior have been extensively studied in animals. Initial studies on the behavioral effects of corticosteroids focussed on adrenal ablation and subsequent hormone replacement therapy. In general, adrenalectomy has not been found to impair the acquisition of an aovidance response in rats (Bohus & Endroczi, 1965; Moyer, 1958; de Wied, 1967). In fact, Weiss and colleagues (1970) observed a superior acquisition of both active and passive avoidance behavior in adrenalectomized rats. Hodges and Vernikos-Danellis (1962) have suggested that enhanced performance in adrenalectomized animals is the result of high circulating levels of endogenous ACTH, because glucocorticoid replacement which normalizes the level of circulating ACTH in adrenalectomized animals has been shown to normalize the avoidance response of these animals. However, other studies (van Delft, 1970), while demonstrating an ameliorating effect of adrenalectomy on a pole-jumping avoidance task, found no reduction in performance following administration of dexamethasone, a potent blocker of ACTH release.

During extinction of avoidance, the aversive stimulus is removed, making responding unnecessary. Adrenalectomized rats continued to respond longer than intact animals during the extinction phase (Bohus, Nyakas, & Endroczi, 1968). Conversely, corticosterone-treated rats stopped responding earlier than untreated animals. This effect of corticosteroids does not appear to be solely mediated via suppression of ACTH, since corticosteroids facilitate extinction of active

avoidance in hypophysectomized as well as in intact animals (de Wied, 1974). Finally, both systemic and central administration of a variety of steroids have been reported to facilitate active avoidance extinction (Bohus, 1970; de Wied, 1967).

In contrast to acquisition of active avoidance behavior, glucocorticoids appear to be more effective in modifying passive avoidance behavior. With regard to acquisition of passive avoidance, several studies have demonstrated that pretraining administration of glucocorticoids to intact animals shortens passive avoidance response latencies immediately after training, suggesting an impairment in acquisition. For example, Bohus and coworkers (1970) found that rats given a single dose of cortisone (20mg/kg) three hours prior to training had shorter latencies to re-enter a chamber where they had just been shocked. The effects of the corticosteroids appear to be a function of shock intensity, with more corticosteroids required to suppress passive avoidance behavior as shock intensity increases. Similarly, water-deprived rats treated with cortisol, corticosterone, or 6-dehydro-16-methylene-cortisol resumed drinking in a chamber where they had been shocked more quickly than did controls (Bohus, 1973).

There are also a number of reports suggesting that adrenal hormones impair retention of the passive avoidance response. Adrenalectomized rats perform better than intact rats in passive avoidance retention tests, demonstrating longer response latencies, as well as increased defecation (Weiss, McEwen, Silva, & Kalkut, 1970). Moreover, administration of corticosteroids to intact animals causes poorer retention hours and even one day later (Bohus, 1973; Bohus,

Grubits, Kovacs, & Lissak, 1970). Because animals given high doses of corticosteroids show impaired acquisition and retention of passive avoidance behavior, it is not surprising that they stop avoiding earlier during the extinction period. Administration of dexamethasone three hours prior to initial training and each subsequent test session, facilitated the extinction of passive avoidance behavior (Bohus, Grubits, Kovacs, & Lissak, 1970).

The effects of adrenal hormones on appetitive conditioning are not as well understood. While injections of corticosterone in intact rats delayed the acquisition of a spatial discrimination for water reward, performance on a discrimination reversal was enhanced (Bohus, 1973). Appetitive extinction (removal of a positive reinforcer) is known to cause elevation of plasma corticosteroids (Davis, Memmott, McFadden, & Levine, 1976), but the effect of adrenal hormones on performance is less clear. Garrud et al. (1974) reported that administration of 1 mg of corticosterone daily to intact rats facilitated the extinction of a food-reinforced response. On the other hand, adrenalectomy has also been reported to facilitate the extinction of a food-reinforced response, while replacement with corticosterone normalized the behavior of adrenalectomized rats, but was without effect in intact animals (Micco, McEwen, & Shein, 1979).

A number of treatments, including electroconvulsive shock (ECT) and protein synthesis inhibitors, administered shortly after training, have been found to produce retrograde amnesia for training experiences, especially with passive avoidance tasks (Dunn, 1980). In a retention test of passive avoidance, usually given 24 hours or more after

training, the effectiveness of an amnesic agent is determined by a decrease in response latency. Studies conducted on rodents have demonstrated that prior adrenalectomy prevented or attenuated the amnesic effects of intracranial puromycin (Flexner & Flexner, 1970), subcutaneous (SC) cycloheximide (Nakajima, 1975), and ECT (Bookin & Pfeifer, 1978). These studies are difficult to interpret, however. Although it is tempting to conclude that the amnesic effects of these protein synthesis inhibitors is mediated via directs actions on the adrenal gland (Nakajima, 1975), other protein sythesis inhibitors (emetine, aminoglutethimide) which suppress corticosteroid synthesis to the same degree, are not amnesic (Squire, St. John, & Davis, 1976). Thus, the longer latency exhibited by adrenalectomized animals on a passive avoidance task may be due to a reduction in motor activity (Squire, St. John, & Davis, 1976). This hypothesis is partially supported by reports that adrenalectomized animals are less active than intact ones in open field paradigms. In addition, it is difficult to ignore the role that elevated ACTH levels (in response to long-term adrenalectomy) may play, since ACTH analogs administered before retention training have been found to attentuate CO2-induced amnesia for passive avoidance (Rigter,, Janssens-Elbertse, & van Riezen, 1976).

There are several reports of improved retention as a result of corticosteroid administration to intact animals. Cortisol (30mg/kg, SC), given immediately after training, improved performance in cycloheximide-treated mice (Nakajima, 1975) and of ECT-treated mice (Nakajima, 1978). Similarly, post-training injections of dexamethasone (4mg/kg, SC) blocked the amnesic effects of anisomycin for both active

and passive avoidance tasks (Flood, Vidal, Bennett, Orme, Vasquez, & Jarvik, 1978). However, the doses administered in these studies have been supraphysiological, and may elevate plasma levels of corticosteroid severalfold. Squire et al. (1976) observed that a lower dose (1.2 mg/kg), which produced plasma corticosteroid levels more in the physiological range (35 mcg/100 ml), did not block the amnesic effects of cycloheximide for passive avoidance training. Thus, high and low doses of corticosteroids may produce differential effects on amnesia for passive avoidance.

Recent evidence suggests that ACTH and ACTH-like peptides affect avoidance behavior, appetitive behavior, and imprinting in animals. Before reviewing this literature, it is appropriate to discuss methodological issues.

Most research exploring the effects of ACTH on behavior have utilized either classical endocrine ablation or exogenous administration of the peptide. Hypophysectomy removes the pituitary source of ACTH, MSH, beta-LPH, and beta-endorphin, but unless ablation is performed carefully, ACTH-producing cells may remain and proliferate within the sella turcica (Moldow & Yalow, 1978). Additionally, hypophysectomy produces loss of all pituitary hormones, resulting in metabolic disturbances and physical debilitation. Although, pituitary ACTH can also be suppressed by administration of exogenous glucocorticoids or dexamethasone, these steroids may have their own independent actions on behavior. The POMC system can also be lesioned by classical methods, however important neural pathways may also be destroyed.

Peripheral administration of ACTH is also problematic. The half-life of ACTH is relatively short (minutes), so that slow release preparations (e.g., zinc phosphate gels) or analogs (ORG 2766) with amino acid substitutions designed to retard or prevent proteolytic action are sometimes required. Secondary effects (steroidogenic) of the administered peptides must also be considered. The adrenocortical activity of ACTH can be prevented by prior adrenalectomy of the animal, but this not only removes circulating corticosteroids (which may play a "permissive" role), but also depletes mineralocorticoids and peripheral catecholamines, and elevates endogenous ACTH levels. In order to circumvent this problem, ACTH analogs (that supposedly lack adrenocortical activity) such as ACTH 4-10, ACTH 1-10, and alpha-MSH have been used. Unfortunately, these analogs may not exert all the extra-adrenal activities of the entire molecule. A further problem is that these analogs may indeed stimulate adrenocortical steroidogenesis (Brain & Evans, 1977) to a slight, but significant degree. A final confound in these studies is that peptides administered peripherally may enter the brain, albeit in small amounts. Although it has been argued that the blood-brain barrier prevents entry of peptides into the CNS (Cornford, Braun, Crane, & Oldendorf, 1978), a recent study by Rapoport et al. (1980) found significant brain uptake of several labeled opioid peptides. Moreover, many important regions of the brain, including the median eminence of the hypothalamus, do not have a blood-brain barrier, nor does the entire pituitary, the pineal, or the infundibulum.

Studies in hypophysectomized animals have revealed the role of

pituitary hormones on acquisition of learned behavior. Appelzweig and Baudry (1955) first demonstrated that hypophysectomized rats are deficient in the acquisition of active avoidance, and that this deficit could be reversed by chronic treatment with ACTH. De Wied (1964) subsequently replicated this work and showed that this effect is caused by ACTH itself and not through an effect on the adrenal cortex since ACTH analogs, essentially devoid of corticotrophic activities, are fully behaviorally active (de Wied, 1966; de Wied & Bohus, 1966). Under certain conditions, ACTH can facilitate acquisition of active avoidance in intact animals. Pretraining administration of ACTH stimulated acquisition of active avoidance in both intact and adrenalectomized rats ( Bohus, Nyakas, & Endroczi, 1968). These findings were subsequently replicated by Beatty et al. (1970).

Extensive work has also revealed that extinction of active avoidance is facilitated by removal of the entire pituitary or the posterior lobe (de Wied, 1965). ACTH replacement reverses this deficit (de Wied, 1965), and retards extinction in intact rats (Murphy & Miller, 1955). These effects are clearly mediated via extra-adrenal mechanisms because ACTH delays extinction in adrenalectomized animals (Miller & Ogawa, 1962), and since ACTH analogs are fully active (Greven & de Wied, 1973). The minimum sequence for retarding extinction appears to be ACTH 4-7, although recently ACTH 11-24 and ACTH 25-39 have also been found to delay extinction, although tenfold higher doses are necessary (Greven & de Wied, 1973),

The CNS sites for the behavioral actions of ACTH have been studied by microinjection or implantation of these peptides into the brain.

Initial studies implicated the posterior thalamus, since bilateral lesions of the parafascicular nucleus abolished the effects of ACTH 4-10 on conditioning and extinction (Bohus & de Wied, 1967). Moreover, local administration of ACTH 4-10 into the rostral mesencephalon or caudal thalamus resulted in increased resistance to extinction of an active avoidance task (van Wimersma Greidanus & de Wied, 1971). Other regions, including the substantia nigra, posterior hypothalamus, and reticular formation, were ineffective sites. More recently, lesions of the rostral septum, dorsal hippocampus, amygdala, or fornix (van Wimersma Greidanus, Croiset, & Schilling, 1979) were also found to block the effect of ACTH 4-10 on extinction. Taken together, these findings suggest that limbic structures may mediate the behavioral effects of ACTH.

In passive avoidance paradigms, ACTH 1-24 given prior to training improved retention of passive avoidance in rats, but only at low footshock intensities (Lissak & Bohus, 1972). Gold and van Buskirk (1976) showed that post-training injections of ACTH could also facilitate subsequent performance in rats, but that there were interactions between shock intensity and dose of ACTH. An inverted U-shaped dose-response curve emerged, in which moderate doses of ACTH enhanced performance, and high doses inhibited it. At higher shock intensities, when performance was improved, ACTH was only inhibitory. These results were interpreted in terms of hormonal modulation of memory storage; the endogenous release of hormones added to the effects of exogenous ACTH.

ACTH and its analogs also affect extinction of passive avoidance.

Levine and Jones (1965) reported that ACTH prolonged avoidance of a water-reinforced bar press task after punishment. Anderson and colleagues (1968) verified these results in hypophysectomized rats. ACTH-like peptides also reverse amnesia for passive avoidance caused by a variety of agents. Rigter et al. (1975) demonstrated that ACTH 4-10, given one hour before retention (but not before testing), reversed CO2-induced amnesia for passive avoidance. Other investigators have found that ACTH given immediately after training to be effective in reversing ECT-induced (Keyes, 1974) and anisomycin-induced amnesia (Flood, Jarkiv, Bennett, & Orme, 1976). In general, these studies have been interpreted as indicating that ACTH analogs play a role primarily in the motivational aspects of conditioned avoidance behavior. Facilitory effects of ACTH have been most commonly observed when the peptide is administered prior to testing. Since this is unlikely to be specific to the learning, it seems that ACTH may be acting on arousal mechanisms. There is no good evidence for an effect on consolidation of memory or enhancement of retrieval, nor for a specific effect on learning. The extinction data are perhaps the most difficult to reconcile with this interpretation, since delayed extinction can be regarded as perseveration or even the inability to "unlearn" a task.

There is also evidence for an influence of POMC peptides on appetitive behavior. Both alpha-MSH (Stratton & Kastin, 1975) and ACTH 4-10 (Isaacson, Dunn, Rees, & Waldock, 1976) have been reported to facilitate acquisition of complex tasks. However, like active avoidance training, extinction seems to be more sensitive. Extinction of food-deprivation tasks was retarded by alpha-MSH (Sandman, Kastin, &

Schally, 1969), ACTH and its analogs (ACTH 4-10, ACTH 1-24) (Guth, Levine, & Seward, 1971), but enhanced by corticosterone (Garrud, Gray, & de Wied, 1974). Extinction of sexually motivated behavior was also retarded by ACTH 4-10 (Bohus, van Wimersma Greidanus, & de Wied, 1975). With regard to operant behavior, ACTH enhanced conditioned suppression (but only in the morning) (Schneider, Weinberg, & Weisssberg, 1974), acquisition of a lever-pressing response (Guth, Levine, & Seward, 1971), and free operant response (Wertheim, Conner, & Levine, 1967). ACTH also delayed the extinction of frustrative nonreward (Gray & Garrud, 1977). This effect closely resembled that on the extinction of active avoidance: ACTH 4-10 and ACTH 1-24 delayed extinction, whereas corticosterone had the opposite effect.

Effects of ACTH have been reported in a variety of species other than rodents. Enhancement of learning or habituation responses has been reported in lizards (Stratton & Kastin, 1975), toads (Horn, Greiner, & Horn, 1979), and beetles (Shelman, Ponomareva-Stepnaya, Maksimova, Nezovibati'ko, & Ashmarin, 1978). ACTH may also have a physiological role in imprinting behavior in birds. Alterations in the HPA system of Pekin duckling embryos by injecting ACTH, produces a dose-dependent effect on imprinting behavior: small doses facilitate following, whereas large doses have no effect (Martin, 1973; 1975). Moreover, the developmental rise in corticosterone following hatching has been found to coincide with the imprinting sensitive period (Weiss, Koehler, & Landsberg, 1977). Landsberg and Weiss (1976) reported that stress or ACTH administration inhibited imprinting in ducklings, an effect they attributed to corticosterone. Doses which blocked

imprinting behavior in this study were associated with increased corticosterone levels, whereas doses that failed to affect imprinting also failed to elevate corticosterone levels. Interpretation of these findings are difficult since the authors did not differentiate between imprinting preference and response approach intensity. Martin & van Wimersma Greidanus (1979) subsequently designed a study to tease apart the relative contribution of ACTH to both instinctive behavior (approach response) and learning processes (object imprinting). Pekin ducklings, given either corticotrophic (ACTH 1-24) or non-corticotrophic (ACTH 4-10, ACTH 1-10) analogs of ACTH were tested under two conditions: (1) during initial exposure to a stimulus (simulating the instinctive approach response); and (2) during a preference test in which they were to choose between the initial imprinting object or a novel object (measuring learning processes). Their results indicate that none of the ACTH molecules had strong effects on the learning component of imprinting. Rather, the non-corticotrophic ACTH fragments, i.e., ACTH 1-10 and ACTH 4-10 facilitated the imprinting approach response. ACTH 1-24 (which is even more effective in releasing corticosterone than the endogenous ACTH 1-39) did not affect the ducklings' approach response. Taken together, these findings suggest that ACTH stimulates filial approach behavior which leads to imprinting. Failure of ACTH 1-24 to impact on either the approach response or the imprinting process was attributed to its potent effect on stimulating corticosterone secretion.

Pituitary-adrenal hormone influences on <u>human</u> cognition are less clearly defined. The impact of endogenously administered

corticoteroids on human cognitive function has generally been inferred from anecdotal reports of diminished cognitive performance and affective disturbance (initially euphoria, but over a period of time, depression) in patients receiving steroids as palliative therapy (Hall, Popkin, Stickney, & Gardner, 1979; Haskett, 1987; Varney, Alexander, & MacIndore, 1984). Few studies have systematically explored this relationship, but a study is currently underway in our laboratory.

Effects of ACTH and like peptides (alpha-MSH, vasopressin) on human performance are in agreement with animal studies which suggest that ACTH-like neuropeptides influence attention (Bohus, 1979). Studies conducted in humans have generally focussed on two populations: normal volunteers and mentally impaired patients (normal elderly subjects, psychiatric patients, demented/retarded individuals).

Endroczi and colleagues (1970) were the first group to demonstrate that ACTH had behavioral effects in humans. When this neuropeptide was administered to normal volunteers, it caused attenuation of habituation to a repeated sound stimulus. Subsequently, Kastin and coworkers reported extensively on the effects of ACTH, MSH, and related peptides on behavioral and EEG measures in humans (Kastin et al., 1975). In one of the earliest studies (Kastin et al., 1971), infusion of alpha-MSH resulted in a marked increase in the averaged somatosensory cortical evoked response during relaxation. This effect was even more marked during attention. Although verbal retention was not affected, administration of alpha-MSH enhanced visual retention. As recently reviewed (Kastin et al., 1975), the administration of MSH 4-10 (which is structurally identical to ACTH 4-10) to 20 normal males enhanced

visual discrimination and retention. These two measures can be considered sensitive indicators of the state of attention of the subject. Spatial perception was also improved. This same group has studied the effects of administration of ACTH 1-24 or ACTH 1-10 on a variety of electrophysiological (EEG, visual evoked potential) and neuropsychological measures of attention, memory, and anxiety during a dysjunctive reaction time paradigm (Miller, Kastin, Sandman, Fink, & van Veen, 1974). In this study, an intravenous injection of either ACTH 4-10 or ACTH 1-24 was administered to 20 male medical students prior to a testing session in which the volunteers were required to discriminate between two warning signals before making the appropriate response. Although ACTH 1-24 had no effect on any of the measures examined, ACTH 4-10 did improve performance on the Benton Visual Retention Test (visual memory), while concomitantly decreasing anxiety levels. Moreover, whereas ACTH 4-10 did not influence reaction time, it did alter the visual evoked potential (by increasing the latency and decreasing the magnitude of the negative component occurring at 200 msec), in a manner consistent with increased attention. Several parameters were not affected by the peptide, including measures of emotionality, reaction time, verbal memory, and short term memory for digits. These results with ACTH 4-10 were confirmed by Sandman et al. (1975), again using male subjects. However, in a study where female subjects were used (Veith, Sandman, George, & Stevens, 1978), visual memory was not increased, but verbal memory was, and anxiety was not decreased. In order to assess whether the effects of ACTH on attention were related to endogenous hormone levels, women were studied during

their menstrual phase (plasma ACTH is low) or during midcycle (plasma ACTH is high). Verbal memory was slightly but not significantly better in women during ovulation compared to menstruation when given placebo. ACTH administration significantly improved verbal memory during menstruation, but impaired a visual reversal discrimination task in these women. These results are consistent with behavioral studies in rats and electrophysiological studies in humans. Data from rat studies indicate that MSH enhances visual attention only in males. Conversely, spatial abilities appear to be augmented by MSH in females (Beckwith, Sandman, Hotherall, & Kastin, 1977; Champney, Sahley, & Sandman, 1976). Electrophysiological data have also shown that men and women are differentially influenced by MSH/ACTH fragments. Evoked potentials for the left hemisphere appear to be enhanced in men, whereas potentials from the right hemisphere are affected in women (Sandman & Kastin, 1981). In a study designed to further examine sex differences (Ward, Sandman, George, & Shulman, 1979), both males and females showed equivalent improvement with ACTH 4-10 on an item recognition test, and there was no effect on anxiety. These findings are consistent with data from Gaillard and Varey (1979), in which no sex differences were detected.

Subsequent studies by Sandman and colleagues support the hypothesis that ACTH 4-10 enhances attention. In the first of these studies (Sandman, George, Nolan, van Riezen, & Kastin, 1975) subjects were given ACTH 4-10 (15 mg iv) over a 4 hour period. During initial training, subjects were required to make a visual discrimination between two stimuli differing in form and color. Color served as the

salient stimulus dimension in this part of the paradigm. During testing, another color was made the "correct response" by the experimenter (intradimensional shift), while later in the test period, form became the relevant stimulus dimension (extradimensional shift). Subjects who were given the heptapeptide were quicker to respond to a change in color (intradimensional shift) than subjects given a placebo, but were significantly slower to change cognitive sets when form became the relevant stimulus dimension (extradimensional shift). This suggests that ACTH enhanced the ability of the subjects to focus on the task at hand, paying careful attention to certain characteristics but not others. The investigators concluded that ACTH 4-10 increased selective attention at the exclusion of other environmental cues. Although these findings are in accord with data from the animal literature, a debate continued as to the action of these peptides. Gaillard and Sanders (1975) suggested that MSH/ACTH 4-10 may improve performance by combatting fatigue and facilitating acquisition of a concept. In this study, normal volunteers given placebo showed only slight improvement in their performance on a repeated serial task during a continuous 30-minute test period. Their learning by repetition was marked by increased errors and slower reaction time during the trial. But, subjects who were given 30 mg of ACTH subcutaneously showed fewer errors and faster reaction times later in the trials. A second study (Gaillard & Varey, 1979), using a potent ACTH 4-9 analog confirmed the hypothesis that ACTH prevents the deterioration of reaction time on a continuous performance task by preventing fatigue. In order to assess whether MSH/ACTH was actually

influencing perceptual threshold or discrimination in previous studies of selective attention (Miller, Kastin, Sandman, Fink, & van Veen, 1974; Sandman, George, Nolan, van Riezen, & Kastin, 1975), eleven male volunteers were subsequently tested with both detection and discrimination procedures while being infused with MSH/ACTH 4-10 or placebo (Sandman, George, McCanne, Nolan, Kaswan, & Kastin, 1977). In the first part of the test (detection trial), stimuli were presented for 6 msec at different levels of brightness. Subjects were required to press one key if they detected a stimulus and another if they did not. Infusion of MSH/ACTH 4-10 raised the threshold for detection and impaired the ability of subjects to accurately report the presence of a stimulus. During the second part of the test (discrimination trial) subjects were required to distinguish between two different sets of stimuli, all of which were above the perceptual threshold. Administration of the peptide enhanced the ability to discriminate between the two stimuli. Taken together, these findings suggest that MSH/ACTH 4-10 facilitates selective attention, while impairing simple intake or detection of threshold stimuli. The authors suggest that perhaps the peptide raised the absolute threshold for stimuli, thereby acting as a "filtering mechanism" to protect the individual from distracting "perceptual noise". However, with suprathreshold stimuli, information processing is enhanced. Additional physiological evidence for an effect of ACTH 4-10 on attention is derived from their finding that ACTH 4-10 not only improved subjects' ability to discriminate between relevant and irrelevant stimuli, but also augmented heart rate deceleration during the presentation of novel stimuli. Finally, Ward,

Sandman, George, and Shulman (1979) examined the effects of ACTH 4-10 on subjects' ability to remember if items presented during a test trial were part of an earlier set consisting of between one and four items. Reaction time was also measured, and data was plotted as a linear function of reaction time and set size. Treatment with ACTH 4-10 reduced reaction time, regardless of the size of the memory set, indicating that ACTH 4-10 facilitates attention to environmental stimuli, rather than memory. In conjunction with data from previous studies, this study suggests that the most parsimonious explanation for the effects of MSH/ACTH 4-10 on human performance appears to be facilitation of attention to environmental stimuli.

Of interest, ACTH does not appear to influence an active conditioned avoidance response in humans (Miller, Fischer, Groves, Rudrauff, & Kastin, 1977), in contrast to results obtained in lower animals. Specifically, normal volunteers were given either ACTH 4-10 or diluent and then taught to avoid an electric shock by pressing a key during a safe interval between a warning light and onset of shock. ACTH did not influence any parameter of the acquisition or extinction phases, indicating that inhibition of extincition of conditioned avoidance does not generalize across species from rodents to humans.

Ferris et al. (1976) have suggested that one possible reason for the limited effects of ACTH 4-10 in normal humans (as compared to rather pronounced effects in animals) may be that normal volunteers are functioning at optimal levels, thereby producing a ceiling upon improvement. Thus, if human subjects with submaximal performance were tested, the effects of ACTH may be more profound. Normal elderly

subjects, demented individuals, psychiatric patients receiving electroconvulsive therapy (ECT), and mentally retarded patients represent categories of individuals whose cognitive abilities may be impaired. As such they can serve as potentially ideal groups to evaluate the effects of MSH/ACTH 4-10.

Normal elderly subjects have been shown to improve slightly or not at all when given ACTH-like peptides. Dornbush and Volavka (1976) found a slight increase in reaction speed, but no overall improvement in mental capacity. In a recent double-blind, placebo-controlled study by the same group (Dornbush, Shapiro, & Freedman, 1981), ACTH 4-9 (the shortest behaviorally active fragment of the ACTH neuropeptide) produced no change in measures of attention or memory, but did produce mood changes described as a "sense of well-being, energy, and drive". The authors suggest that this short chain peptide may be useful in older individuals as a potential antidepressant and mood elevator. Of particular interest in this study was the finding that 25% of the sample (N=3) indicated that the ACTH 4-9 analog had profound positive effects on their near vision, without affecting distance vision. The authors speculated that this type of selective visual improvement in a presbyopic group may be explained by an increase in the eye's accomodative ability. This effect was noticed on the afternoon of drug administration and lasted for several days without additional dosing. A study of mildly senile subjects by Branconnier and colleagues (1979) is only slightly more compelling. Eighteen mildly senile, organically impaired individuals, displayed reduced depression and confusion and increased vigor after treatment with MSH/ACTH 4-10. No change in the

Bender-Gestalt or Wechsler Memory Scale was noticed, but there was a trend toward decreased reaction time in the subjects. The latter finding is probably due to delayed fatigue, consistent with the report of Gaillard and Varey (1979). The authors suggest that the effects observed were evidence of a non-specific arousing effect, but EEG findings of a decrease in the alpha rhythm are not in accord with such reasoning. More recently, Miller, Groves, Bupp, and Kastin (1980) noted improvement in visual retention after administration of MSH/ACTH 4-10 to some elderly patients. This effect was more pronounced in men than in women. Although decreases in ACTH levels in cerebrospinal fluid have been observed in patients with Alzheimer's disease (Facchinetti, Nappi, Petraglia, Martignoni, Sinforano, & Gerazzani, 1984), no improvement in mental performance was observed in 38 female Alzheimer patients given the potent ACTH 4-9 analog, Org 2766 (Martin, Ballinger, Cockram, McPherson, Pigache, & Tregaskis, 1983). However, these patients were very severely demented, and further studies appear to be justified in patients with other types of dementia.

Experiments examining the effects of ACTH 4-10 in psychiatric patients are still very limited, although depressed patients treated with ECT seem to be uniquely suited for studies of attention, concentration, and memory. Such patients have attentional disturbances secondary to the depressive disorder, as well as transient disruption of memory consolidation/retrieval attributable to ECT (Williams, 1977).

In a preliminary study (Small, Small, Milstein, & Dian, 1977) of depressed patients treated with bilateral ECT, no significant differences between ACTH 4-10 and placebo were observed on measures of

immediate and delayed recall. The initial experiment modelled after previous animal experiments, examined performance after a single treatment. There were some indications that ACTH administration facilitated performance in a picture recognition task, in that patients who received the peptide 24 hours post-ictally showed better total scores and fewer errors of commission than those who received placebo. This trend was not statistically significant. In the second experiment, patients received either ACTH or placebo after the fifth or sixth treatment in the series without a seizure between learning and testing. ACTH did not improve performance on any of the measures. Similarly, in a series of experiments, d'Elia and Frederiksen (1980a,b) found no clinically significant effects of ACTH 4-10 on sustained concentration, consolidation of engrams, or enhancement of retrieval in depressed patients receiving unilateral ECT. These findings are in contradiction to animal studies in which ACTH 4-10 has been demonstrated to possess anti-amnesic effects in pre-trained rats given electroconvulsive shock (Rigter & van Riezen, 1975).

Among the most promising effects of MSH/ACTH fragments have been those on the behavior of mentally retarded individuals. Sandman, George, Walker, and Nolan (1976) repeated their visual dimensional shift study in adult mentally retarded men. Intravenous administration of 15 mg of MSH/ACTH 4-10 again improved performance on the intradimensional shift (color). Additionally, treatment with the peptide also improved subjects' ability to recognize that form was the correct stimulus dimension (extradimensional shift). Further, MSH/ACTH 4-10 produced significant improvement on tests of spatial localization,

visual retention, and matching auditory patterns. In a second study (Walker & Sandman, 1979), the influence of an orally administered analog of MSH/ACTH 4-10 (0, 5, and 20 mg) was examined. Although significant improvement in measures of attention were observed, the effects were not as dramatic or pervasive as those observed in the initial study. The authors attributed the attenuation of effects to a number of factors including route of administration, reduced potency of the analog, different doses, etc. In a third study (Sandman, Walker, & Lawton, 1980), the ACTH analog appeared to improve the day-to-day work performance of mentally retarded individuals in a dose-dependent manner. In addition, the drug also enhanced social interaction and communication in these subjects. In contrast to the encouraging findings with mentally retarded subjects, learning disabled and hyperactive children showed no improvement (Rappoport, Quinn, Copeland, & Burg, 1976).

Overall, the results obtained with humans so far do not provide a clearcut picture of the nature of the peptide's activity. At best, MSH/ACTH may enhance attention in normal human subjects. There is no good evidence that these peptides have any effect on consolidation or retrieval of memory. Furthermore, the magnitude of the effects reported are quite small in relation to the effects observed in lower animals. Additional clinical studies are necessary in order to clarify the role of MSH/ACTH in mentally impaired individuals.

In addition to their effects on attention, learning, and memory, ACTH and cortisol have been shown to alter other CNS functions which may impact on neuropsychological performance. For example, running

wheel activity of rats was markedly decreased by adrenalectomy (Leshner, 1971) or hypophysectomy (Richter & Wislocki, 1930), but was restored to normal by injections of corticosterone (Leshner, 1971). In adrenally intact rats, exogenous corticosterone decreased running wheel activity (Leshner, 1971), whereas administration of dexamethasone to the drinking water caused a dose-dependent increase in running behavior of intact animals (Kendall, 1970). At present, these seemingly contradictory responses are difficult to reconcile; however, the stimulatory effect of dexamethasone does not appear to be due to suppression of ACTH secretion, since implantation of cortisol acetate in the median eminence (which also suppresses ACTH secretion), reduces activity (Kendall, 1970).

Glucocorticoid administration had an opposite (depressive) effect on general activity, operationally defined as any body movements that produced vibrations of the home cage mounted on an activity monitoring platform. Dexamethasone in the drinking water significantly reduced daily activity of intact male rats (Katz & Carroll, 1978). The opposing effects of dexamethasone on general vs. running wheel activity support the notion of separate mechanisms controlling these two types of spontaneous activity. Similar results have been observed in other species. For example, treatment with ACTH or corticosteroids inhibits spontaneous goal-directed motor activity in the cat (Lissak & Endroczi, 1964).

Glucocorticoids also affect open-field (a novel empty enclosed area) behavior. Adrenalectomized rodents were more "emotional" than controls in the open-field situation, i.e., they moved around less and

defecated more (Joffe, Mulick, & Rawson, 1972). Conversely, injections of cortisone acetate in intact mice stimulated open-field within two days of starting treatment (Fuller, Chambers, & Fuller, 1956). Although this latter finding has been amply replicated, Stern and colleagues (1973) found no reliable correlation between physiological levels of corticosteroids and open-field behavior.

Glucocorticoid effects on CNS electrical activity have been extensively explored, but differences in methodology (types of steroid; routes of administration) make direct comparisons among these studies difficult. Systemic injection of cortisol to intact, freely moving rats increased the spontaneous firing rate of neurons in the anterior hypothalamus and mesencephalic reticular formation, but decreased activity in the ventromedial and basal hypothalamus (Phillips & Dafny, 1971). Similarly, iontophoretic application of dexamethasone onto medial basal hypothalamic neurons in intact animals produced an immediate attenuation of cell firing rate, as did direct application of dexamethasone to mesencephalic neurons (Steiner, Ruf, & Akert, 1969). The difference between this latter finding and that of Phillips and Dafny (1971) is not surprising, because systematically administered hormones may only affect cells indirectly. The effect of administered glucocorticoids on hippocampal neurons in intact animals is perhaps most germane to this paper, since the hippocampus has been implicated in learning and memory functions, as well as in modulating the HPA response to stress. Following systemic injection of cortisol in rats, 56 percent of the hippocampal neurons observed responded with either an increase or decrease in spontaneous firing rate (Phillips & Dafny,

1971). However, systemic administration of corticoids into animals with intact pituitaries may confound the steroid effect with possible effects mediated by feedback inhibition at both pituitary and hypothalamic levels. On the other hand, iontophoretic application of either cortisol or corticosterone produced no change in spontaneous activity in any of the 500 neurons tested by Barak and coworkers (1977), whereas injection of dexamethasone into the vicinity of the recording electrode produced an immediate and marked decrease in multiple unit activity (Michal, 1974). Effects of corticosteroids on evoked neural activity have also been reported. In intact control animals, stimulation of the sciatic nerve increased firing rates of individual neurons in the anterior hypothalamus, whereas administration of cortisol resulted in decreased firing rates of these neurons following stimulation (Feldman & Dafny, 1970). In adrenalectomized rats, injection of corticosterone slowly increased the amplitudes of hippocampal potentials evoked by visual or somatosensory stimulation (McGowan-Sass & Timiras, 1975). This data suggests the possible alteration of neuronal responses to sensory input by corticosteroids, a topic amply studied and reviewed by Henkin (1975).

Sensory processes have been found to be disrupted in conditions of both hypo- and hypersecretion of adrenocortical steroids (Henkin, 1975). Patients with Addison's disease (primary adrenocortical insufficiency) exhibit dramatic increases in their ability to detect olfactory, gustatory, and auditory stimuli. Some individuals also showed a lowered threshold for pain. Treatment with glucocorticoids returned detection sensitivity to within normal limits in 24 to 48

hours. In contrast, patients with Cushing's syndrome (hypercortisolism of adrenal origin) exhibited decreased detection sensitivity for odor, tast, and sound. Variations in glucocorticoid secretion within the normal range may also influence sensory processes, since the circadian pattern of detection sensitivity closely parallels the pattern of cortisol secretion. Although detection sensitivity appears to be altered in opposite directions by increases or decreases in cortisol level, conditions of hypo- and hyper-cortisolism both result in diminished recognition sensitivity. For example, both groups experience difficulty in identifying specific taste qualities, such as bitter and salty, at low concentrations, and understanding speech in the absence of extraneous cues. This finding suggests that the ability of humans to integrate sensory information is impaired by deviations of glucocorticoid levels above or below optimal limits.

Present Study and Hypotheses

Increased activity of the hypothalamic-pituitary-adrenocortical axis (HPA) is a prominent feature in a significant proportion of patients with major depressive disorder. Alterations in the activity of CNS neurotransmitters and limbic system "overdrive" represent potential sources of dysfunction which may produce this hypercortisolism in depressed patients, as well as associated affective and cognitive symptomatology. The effects of prolonged HPA dysfunction are of no less interest than its cause. Previous studies have documented varying degrees of affective, vegetative, and cognitive disturbances in patients with either spontaneous (Cushing's syndrome), psychogenic (anorexia nervosa) or iatrogenic forms of hypercortisolism, but interpretation of these findings have been complicated by the serious metabolic complications accompanying these conditions. Depressed patients represent an excellent population in which to explore the clinical concomitants of HPA dysfunction, because cortisol levels are elevated for prolonged periods without the presence of secondary metabolic disturbances.

The major objective of the present study was to investigate various measures of HPA activity in a group of depressed inpatients, in order to attempt to elucidate the relationship between cortisol/ACTH perturbations and neuropsychological functioning. The complexity of HPA physiology militates against the use of singular measures of the system's activity in exploring such a relationship. Therefore, both basal (plasma cortisol and ACTH, urinary free cortisol), and challenge measures (dexamethasone suppression test) were used to identify

biological subgroups of depressed patients. Similarly, the neuropsychological tests selected for inclusion in this study sampled a wide range of cognitive and motor functions.

The main experimental hypothesis tested was that depressed patients with feedback abnormalities (DST nonsuppressors) would perform more poorly than depressed patients without measurable feedback disturbances (DST suppressors) on a variety of neuropsychological tasks. Specifically, DST nonsuppressors would show both a greater degree of impairment on individual tests and impaired performance on a larger number of cognitive measures than DST suppressors.

The full significance of glucocorticoid influences upon cognitive functioning can be better understood by determining the degree to which variance in specific aspects of neuropsychological performance among individuals is related to variance in brain exposure to cortisol. In order to do this, it is necessary to incorporate a measure of cortisol that reflects tissue exposure over time, rather than momentary total circulating cortisol concentrations. Twenty-four hour collection of urinary free cortisol was the obvious choice to satisfy these requirements. The second major hypothesis was that UFC hypersecretors would be significantly more impaired than UFC normosecretors on a number of neuropsychological variables. Furthermore, since UFC excretion provides a better reflection of CNS exposure to active glucocorticoid than individual plasma measures, we would expect a more robust correlation between UFC levels and cognitive dysfunction than between any of the individual basal plasma indices and cognitive dysfunction.

Next, the relationship of ACTH levels to cognition was explored. Although the literature suggests that acute administration of non-steroidal fragments of ACTH may act on arousal mechanisms to enhance attention, data obtained from patients with pituitary-dependent Cushing's disease (i.e., having high levels of both ACTH and cortisol) provide evidence to the contrary. This differential effect may be due in part to the steroidogenic effects of endogenous ACTH, although extra-adrenal actions and chronicity of plasma elevations must also be considered. Based on this latter data, depressed patients with high ACTH levels would be expected to show more severe deterioration in cognitive functioning that those with lower ACTH levels.

A number of ancillary hypotheses follow from the above. First, based on relevant data in Cushing's syndrome and anorexia nervosa patients, I would expect that cognitive impairment would be most profound in tests reflecting non-verbal, visual-spatial, visual-ideational, and psychomotor performance. Second, a substantial body of evidence suggests a positive association between aging and HPA dysregulation (basal cortisol, UFC excretion, post-dexamethasone cortisol levels, DST nonsuppression) in depressed patients. This relationship appears to be state-dependent and is not noted in control populations. Consistent with these findings, one might expect age to be related to neuroendocrine perturbations in this group of depressed patients. Third, limiting data analyses to the simple concepts of "suppressors" vs. "nonsuppressors", without providing referent values may obscure valuable information. For state-related variables such as the DST, we might expect that the more severe the underlying

pathophysiology, the higher the absolute cortisol value following dexamethasone. Thus, correlational analysis of post-dexamethasone cortisol level with degree of cognitive impairment, may provide a better reflection of the actual association, than using the dichotomous categorization for each patient.

Finally, data from my original pilot study (N=25) indicated that cortisol hypersecretion might be of importance as it relates to the subjective experience of impaired cognitive function and overall depressive symptomatology in depressed patients. This is in contradiction to most studies in the literature, though these studies base their presumption of severity on "objective" measures such as Hamilton Depression Scale Scores (or other interviewer-rated scales), which are typically heavily loaded for vegetative symptoms. Based on the preliminary data, I hypothesized that patients with feedback disturbances (specifically, DST nonsuppressors) would show greater severity of illness (and perceived cognitive impairment) than depressed patients with normal feedback inhibition (DST suppressors) on a number of measures other than the Hamilton: (1) self-rating scales (Beck Depression Inventory, Raskin Mood Scale); (2) primary treatment modality chosen by the hospital staff (ECT vs. medication); (3) family history (since we would expect individuals with a biological predisposition to perform more poorly); (4) number of previous admissions; (5) length of hospitalization during current episode.

# CHAPTER 2

## METHOD

### SUBJECTS

Subjects were 63 individuals selected from consecutive admissions over a two-year period to the Payne Whitney Psychiatric Clinic, New York Hospital/Cornell University Medical Center. All of the subjects met DSM-III (American Psychiatric Association, 1980) criteria for major depressive disorder, based upon psychiatric intake evaluation. Inclusion of subjects in to the study was based upon three independent assessments of the subjects' psychiatric status: (a) initial diagnosis by the supervising attending psychiatrist at the time of hospital admission, (b) re-evaluation by a research associate (C.S.) and senior staff psychiatrist, using a semi-structured interview, and (c) a Hamilton Depression Rating Scale (HDS) total of greater than 14 points (Sotsky & Glass, 1983). Patients were excluded or dropped from the study if they did not meet all three inclusion criteria, were unable or unwilling to cooperate with all aspects of the study, or if the original psychiatric diagnosis was changed during inpatient treatment. Based on these criteria, 60 of 63 subjects were included in the final data analyses. One subject was excluded because she had been institutionalized for mental retardation during her childhood. Two other subjects were excluded because they had refused venipuncture and neuropsychological testing. Of the remaining 60 subjects, 14 of the subjects (23.3%) were men and 46 (76.7%) were women. Their mean age was 50.5 years (range 20-84, SD 17.2), and mean level of education was 13.4 $\pm$ 3.2 years. By DSM-III criteria, 48 were diagnosed major

depressive disorder (29 with melancholia, 8 with mood-congruent psychotic features), 2 bipolar disorder, mixed, and 10 bipolar disorder, depressed. The average number of psychiatric admissions for the group was 1.4 $\pm$ 1.8, with 35 of the subjects (58.3 %) having had at least one previous psychiatric hospitalization. Subjects were free of medical conditions known to alter pituitary-adrenal activity, and were not taking drugs known to affect dexamethasone metabolism or response to dexamethasone. The medical and technical factors that may render DST results invalid (Carroll et al., 1981) are outlined in Table 1 (Appendix A). In addition, subjects with evidence of motor disability (tardive dyskinesia, Parkinsonism, severe arthritis, etc.) or visual or auditory impairments known to interfere with results of the neuropsychological testing were excluded. Individuals with mental retardation or a history or obvious symptoms of neurological disease such as strokes, tumors, or serious closed head injury, were similarly excluded. Although most of the subjects had been drug-free for several days at the time of testing, the presence of psychotic symptoms, agitation, acute suicidality, poor food/fluid intake, or limited insurance coverage necessitated the initiation of treatment in some cases. Thus, 10 subjects were on tricyclic antidepressants (mean dose 71.3 mg, imipramine equivalent), 2 on lithium (mean dose= 450 mg), 3 on neuroleptics (mean dose= 66.7 mg, chlorpromazine equivalent), and 2 on short-acting benzodiazepines (mean dose= 5 mg, diazepam equivalent). Low dosages such as these are not likely to significantly impair cognitive functioning (Heaton & Crowley, 1981).

## INSTRUMENTS

### Neuropsychological assessment

The clinical neuropsychology literature indicates that several different approaches to assessment are currently in use. For example, in three recent national surveys of practicing clinical neuropsychologists, it was found that 31% tend to use the Luria-Nebraska Neuropsychological Battery, 34% use the Halstead-Reitan Neuropsychological Battery, and 35% use a variety of measurement instruments not classifiable as a standardized battery (Hartlage, Chelune, & Tucker, 1981; Hartlage & Telzrow, 1980; Seretny, Gray, Hartlage, & Dean, 1985). The neuropsychological battery in the present study was designed to assess a broad array of the types of cognitive functions that are frequently affected by CNS disease. Testing was not conducted as a diagnostic enterprise, but for descriptive purposes. In selecting tests for this protocol, I attempted to strike a balance between an exhaustive examination of cognitive functions and inclusion of measures which have previously been found to be impaired in depressed patients (e.g., concentration, constructional abilities, memory, psychomotor speed). When formulating this battery, the following guidelines were taken into consideration: (a) the tests were sufficiently standardized to allow accurate assessment of whether a given individual fell within the range of normal variation given the subject's age, sex, and general intelligence; (b) the tests had previously been validated on populations of brain-damaged and hospitalized control patients; (c) the tests were readily available and in extensive use in neuropsychological settings; (d) the tests

were ones with which I had some previous clinical experience; and (e) administration time for the entire battery could be limited to between two and three hours across two testing sessions, to minimize patient fatigue.

With the above-mentioned criteria in mind, the following tests (copies/examples included in Appendix B) were chosen:

1-4. Subtests from the Wechsler Adult Intelligence Scale (WAIS-R).

The Wechsler Adult Intelligence Scale (WAIS) was first published in 1955, and was subsequently revised (WAIS-R) in 1981. In general, the WAIS has been repeatedly shown to correlate well with other measures of general intelligence, such as the Wechsler-Bellevue and the Stanford-Binet. In fact, the WAIS (and its revision) is now the most widely used test in assessment of higher intellectual functions, and it provides the IQ norms against which other neuropsychological tests are compared. The WAIS-R consists of 11 subtests, of which the following were used in the present study: Vocabulary, Digit Span, Digit Symbol, and Block Design. These tests were selected as representative of general intelligence, short-term memory, psychomotor speed, and visual-spatial constructional ability, respectively. The scores from most subtests are presented in an age-scaled form in the present study, except where raw scores may be of particular interest, in which case both scores are utilized in data analyses.

The Vocabulary scale consists of 35 words, arranged in order of difficulty, that the subject is asked to define. Correct responses are scored according to quality of response, with content-impoverished responses receiving less credit. The Vocabulary subtest has been

identified as providing one of the best estimates of both verbal IQ and general intelligence, correlating between .8 and .9 with the latter measure (Zimmerman & Woo-Sam, 1973). In addition, this subtest is somewhat less sensitive to left-hemisphere lesions than other verbal subtests, and is one of the subtests least affected by diffuse or bilateral brain dysfunction (Gonen & Brown, 1968). Thus, Vocabulary scores in the present study can provide valuable information about estimated premorbid intellectual functioning. Patients with an age-corrected scale score of less than 6 on this subtest were excluded from participation in this study.

The Digit Span subtest is comprised of two parts, each involving the presentation of increasingly longer random number sequences, that are read aloud at the rate of one number per second. Digits Forward is administered first, and the subject's task is to repeat each sequence exactly as it is given. The examiner continues reading the next longer number sequence (ranging from 3-9 digit spans) until the subject fails a pair of sequences, or repeats a nine-digit sequence accurately. For Digits Backward, the subject must repeat the number sequence in reverse, and the presented spans range from two to eight digits.

Although the scores from these two tasks are combined to obtain one score for the subtest, Digits Forward and Digits Backward involve somewhat different mental operations (Lezak, 1983). Digits Forward is a measure of immediate auditory memory span and attention, and tends to be relatively stable with advancing age. Digits Backward is a measure of active or working memory, involving both the storage and manipulation of information. The Digits Backward span typically

decreases with aging. Variations from the expected pattern of Digit Span Forward/Digit Span Backward (e.g., forward approximately two digits greater than backward) are suggestive of attention, concentration, or sequencing problems, reflecting either a structural or functional disturbance. Impairment was defined as a total scale score less than 6 on the two tasks combined (Wechsler manual, 1981), or a raw score less than 4 on Digits Forward (Spitz, 1972) or less than 3 on Digits Backward (Botwinick & Storandt, 1974).

The Digit Symbol subtest is a symbol-number substitution task consisting of four rows of divided boxes (100 in all). Each box has a randomly assigned number (1 to 9) in the top half, and a blank space in the bottom half. Above the boxes, there is a separate key in which each of the numbers is paired with a simple specific geometric design. The subject's task is to fill in as many of the blank bottom spaces as possible with the symbol it is paired with in the key. The subject is encouraged to work as quickly as possible. The raw score is the number of boxes correctly filled in within 90 seconds.

Digit Symbol is a psychomotor performance test that requires motor speed, persistence, visual-motor coordination, and sustained attention (Lezak, 1983). It is very sensitive to brain damage regardless of the locus of the lesion, and is relatively unaffected by intelligence, memory, or learning (Murstein & Leipold, 1981). A scale score of less than 6 (WAIS manual, 1981) was considered to be impaired in the present study. In addition, age-scaled norms from the Symbol Digit Modalities Test (Smith, 1968, 1973) were used to assess impairment, based on raw scores (# of filled-in boxes). Norms for the Symbol Digit Modalities

Test are given in Appendix C. This test is similar to the Digit Symbol subtest, except that the symbols are given, and the subject is required to fill in the corresponding numbers.

The Block Design subtest requires the subject to assemble red-and-white blocks in a two-dimensional pattern as presented in a test booklet. Ten designs are presented in order of difficulty, with the first five requiring use of four blocks (two-by-two matrix), and the last five requiring nine blocks (three-by-three matrix). The test is timed, and no formal credit is given for partial completion of a design at the time limit.

Block Design is a measure of visual-spatial construction organization, and is sensitive to brain damage in general. However, it is most strongly affected by non-dominant, right-hemisphere lesions, especially where there is parietal lobe damage, or with diffuse loss of cortical neurons, as in Alzheimer's disease (Lezak, 1983). The criteria for impairment on the Block Design subtest employed in the present study is a scale score less than 7, or a score that is 4 or more points below the Vocabulary subtest score (Matarazzo, 1972).

5. Trail making test.

The trail making test is a timed paper-and-pencil test with two parts. Part A consists of circled numbers randomly scattered over a sheet of 8 1/2" X 11" paper. The subject is instructed to connect, in order, consecutively numbered circles. Part B includes both circled numbers and circled letters, and the subject's task is to alternate between numbers and letters in serial order (e.g. 1--A--2--B etc.). On both parts, the subject is instructed to work as quickly as possible

without lifting the pencil from the paper. Scoring consists of the amount of time needed to complete Parts A and B (up to three hundred seconds for each) and the number of errors on each trial (range = 0-25).

The trail making test is one of the most widely used screening tests for brain damage, because it is easy and quick to administer, objectively scored, and sensitive to the effects of cortical lesions (Reitan, 1955, 1958). Trail Making Part A provides a measure of attention and concentration, in conjunction with visual-motor, conceptual-tracking, and sequencing skills. Part B also measures attention and concentration, but involves more complex sequencing skills, where cognitive flexibility is important. When establishing impairment criteria for any test in which response speed contributes significantly to the score, allowances need to be made for the normal slowing effects of aging. Although there is not complete agreement among neuropsychologists regarding aging effects upon trailmaking (Boll & Reitan, 1973; Davies, 1968), the age-based norms (Davies, 1968) will provide a basis for performance in the present study to reduce the possibility of misclassification. The criteria for impairment on the trail making test are outlined in Appendix C. Another variable which appears to be related to trail making performance is intelligence; however, ability-based norms are not available.

6. Rey Auditory Verbal Learning Test (AVLT).

The AVLT (Rey, 1964) is a brief, easily administered test that consists of a 15-item word list that is read aloud to the subject for five consecutive trials. A copy of the Rey AVLT word list is included

in Appendix B. After each of trials one through five, the subject is asked to recall as many words as possible. The recalled words, their order of recall, and any intrusion errors are recorded. Trial six is an interference trial, in which a second 15-item list is presented in the same manner as the first list, followed by free recall of that list. A seventh trial is then given in which the subject is asked to recall as many words as possible from the original list, without hearing the list repeated. Finally, a word list that incorporates all the words from the first and second lists, as well as synonyms and homonyms of these words is presented, and the examinee is required to identify any words recognized from the original list only. Thus, the Rey measures immediate memory span for recall of verbal material (Trial 1), short-term verbal memory following subsequent repetition (Trials 2-5), verbal learning, susceptibility to proactive (Trial 1 minus Trial 6) and retroactive (Trial 5 minus Trial 7) interference, and long-term recognition of visually presented material (Lezak, 1983). The impairment criteria for the Rey AVLT (Query & Megran, 1983) are presented in Appendix C.

7. Category Test.

In its original form (Halstead, 1947), 208 items, comprised of four stimulus figures each, are projected onto a secreen. Six sets of items, each organized on the basis of different principles, are followed by a seventh set comprised of previously displayed items. The subject is instructed that the object of the test is to see how well he or she can learn the concept, principle, or idea that underlies the geometric forms in each of the seven subgroups (sets). Correct

responses are "rewarded" by a pleasant chime, whereas incorrect responses are followed by a buzz. The test is scored for total number of errors. However, this standard form of the Category Test has a number of drawbacks including the cost of the equipment, the difficulty in transporting equipment, and the fact that administration of all seven subtests is time-consuming (up to two hours) and fatiguing to neurological and psychiatric patients (Lezak, 1983). A shortened form of this test (Calsyn, O'Leary, & Chaney, 1980), using the first four sets of the test in booklet form, was adapted for use in the present study, and took between 20 and 30 minutes to administer to most patients. An example from one of the subtests is included in Appendix B. Error scores from the abbreviated form of the Category Test have been found to correlate .89 and .88 with error scores on the standardized version, in validation and cross-validation studies, respectively. In order to evaluate performance on the shortened version based on accustomed norms, the error score is converted by multiplying it by a factor of 1.4 and adding 15 (Lezak, 1983). A cutoff criteria of 50 errors was used to compute impairment scores (Matarazzo, Wiens, Matarazzo, & Goldstein, 1974).

The Category Test is a nonverbal test of abstract reasoning, logical analysis, mental flexibility, and conceptual-problem solving ability, as well as a good predictor of every-day problem solving abilities. It requires visual-spatial perception and color discrimination abilities, as well as effective learning skills.

8. The Stroop Color-Word Test.

The Stroop Test consists of three pages, each with 100 items

arranged in five columns of 20 items each. On the first page are color words (red, green, blue) randomly arranged and printed in black ink. Subjects are asked to read as many of the items as they can in 45 seconds. Page 2 consists of XXXX's printed in either red, green, or blue ink. Subjects are required to identify as many colors as they can in 45 seconds, working down each column. The last page consists of the words from the first page printed in the ink colors from the second page, however, no words are printed in the color ink that they represent (e.g., the word "red" can be printed in blue ink, but not red ink). On this page, the subjects are instructed to name the color of the ink that the word was printed in (rather than read the word) as quickly as they can for 45 seconds. Subjects receive four scores: (1) word naming score; (2) color-naming score; (3) color-word naming scores; and (4) estimated color-word naming score (based on subjects reading and color-naming speeds -- pages 1 and 2). All scores are then age-adjusted and converted to t-scores. A t-score less than 40 on any of the measures is considered impaired (Golden, 1976).

The Stroop measures the subject's ability to shift perceptual set to conform to changing demands (Lezak, 1983), as well as freedom from distractability.

9. Purdue Pegboard Test.

For this test, subjects must place small pegs into a flat board containing pre-drilled holes. The test is administered in three trials. Before beginning, manual dominance is determined (patient self-report) and recorded. During the first trial, the subject is instructed to place one pin at a time in the right-hand row of the

board using the right hand, starting with the top hole and working in sequence. Speed and accuracy are encouraged. During the second trial, this procedure is repeated, using the left hand, and left row of the board. The third trial involves placement of pegs with both hands simultaneously. The time allotted for each trial is 30 seconds. The number of pegs correctly placed is recorded for the right and left hands, and the number of pairs placed correctly is recorded for the simultaneous trial. The cutoff scores for predicting brain damage (Vaughan & Costa, 1962) are age-related, and are presented in Appendix C. For all subjects, cortical damage is likely whenever the score obtained by the nondominant hand exceeds that of the dominant hand by more than three points (Lezak, 1983). Unilateral slowing is suggestive of a lesion in the contralateral hemisphere, whereas bilateral slowing is indicative of bilateral or diffuse encephalopathy.

The Purdue Pegboard Test assesses fine-motor dexterity and accuracy, eye-hand coordination, and motor speed, and is a reliable indicator of the presence and laterality of cerebral lesions (Costa, Vaughan, Levita, & Farber, 1963), independent of educational achievement.

10. Finger-Tapping Test.

The Finger-Tapping Test from the Halstead-Reitan Battery is one of the most widely used tests of manual dexterity (Lezak, 1983). This test requires the subject to tap as rapidly as possible with their extended forefinger on a telegraph key-like lever attached to a mechanical counter. Five 10-second trials are run with both the right and left hands, with brief rest periods between each trial. The score

for each hand is the average for the five trials. The criterion for impairment is less than 50 taps with the preferred hand, or less than 45 taps with the nonpreferred hand (Pauker, 1977). Finger Tapping is a test of motor speed and coordination and allows for comparison of relative performance with right and left hands. Like the Purdue Pegboard, lateralized lesions generally, but not always, show up as a decrease in tapping rate of the contralateral hand (Finlayson & Reitan, 1980).

11. Paced Auditory Serial Addition Test (PASAT).

The PASAT consists of a standardized tape-recorded verbal presentation of a series of single-digit numbers that are presented at a progressively more rapid rate across four series of trials (from 2.4 to 1.2 seconds between numbers). Only the 2.4 and 2.0 second intervals were used in the present study. The subject's task is to add each number to the number immediately preceding it. For example, given the series "1, 2, 6, 8", the subject should respond "3" after the number "2", "8" after the number "6", and "14" after the number "8". The score is total correct (out of a possible 60) at each pacing speed. A score of less than 40 correct responses at 2.4 second pacing, or less than 33 correct at 2.0 second pacing was used as the impairment cutoff (Gronwall & Wrightson, 1974). The PASAT is a sensitive measure of rate of information processing as well as sustained attention, concentration, and conceptual tracking (Lezak, 1983). Many of the depressed patients in the present study found even the 2.4 second trial difficult and anxiety-provoking, and refused to complete the task. Data from these subjects are not included in the analysis.

12. Benton Visual Retention Test (BVRT).

The Benton is a pencil-and-paper test involving the presentation of a series of 10 cards, each containing one to three geometric designs (sample card illustrated in Appendix B). The patient is required to look at each card, and then to reproduce the design from memory after the card is removed. There are four standard administration procedures and three equivalent forms of the test. Administration A provides for a 10-second exposure, followed by immediate recall; Administration B is similar to A except that it has only a 5-second exposure; Administration C is a direct copying test with no memory involvement; and Administration D has a 10-second exposure followed by a 15-second delayed recall. Each administration is scored for both total number of correct designs and total errors. Six types of errors are scored: omissions, distortions, misplacements, perseverations, rotations, and size errors, and more than one error can be recorded for each card.

Administrations A and D were included in the present study. The average loss from D to A by brain-damaged patients has been reported as 0.7 (Benton, 1974), however, the 15-second delay can result in gross memory impairment in some subjects (Lezak, 1983). Conversely, subjects who make fewer errors on the delayed administration (D) than on the immediate recall administration (A), may be suffering from disturbances in attention or concentration, rather than memory per se, or may require additional time to consolidate new information into memory (Lezak, 1983). The age- and IQ-based norms (Benton, 1974) for expected number of correct responses and expected error scores are outlined in Appendix C.

The Benton measures many different cognitive capacities such as overall attention and concentration, visual inattention, visuomotor response, visuospatial perception, immediate memory span, and visual and verbal conceptualization (Lezak, 1983). Thus, it is not surprising that is is quite sensitive to the presence of brain dysfunction, and is useful in differentiating patients with psychiatric disorders from those with organic dysfunction (Benton, 1974; Marsh & Hirsch, 1982).

13. Babcock Story Recall Test.

The Babcock Story Recall Test (Babcock & Levy, 1940) is a 21-unit story (see Appendix B), used to measure immediate and delayed recall. After reading the paragraph to the subject, the subject is instructed to "Tell everything you can remember of the story". Responses are recorded verbatim, and one point is given for each unit correctly recalled. In general, the substitution of one expression for another is not penalized, as long as it does not alter the general meaning or details of the story. Immediately following the first recall trial, the subject is instructed that the same story will be repeated by the examiner and that he/she will be asked to recall it again. The second recall trial comes after approximately 20 minutes of other testing. Four points are added to the immediate recall score to equate for the second presentation of the paragraph before the delayed recall trial. IQ-based impairment criteria for performance on the Babcock Story Recall Test (adapted from Rapoport, Gill, & Schafer, 1968) are listed in Appendix C.

Although the Babcock is generally considered a measure of verbal memory, successful performance also requires adequate attention and

concentration, as well as the ability to "maintain sets or anticipations", and overall intactness of verbal functioning (Rapoport, Gill, & Schafer, 1968).

14. Ammons Quick Test.

The Ammons Quick Test (Ammons & Ammons, 1962) is a standardized intelligence test in three forms, based on perceptual-verbal performance, and requiring only three to ten minutes to administer in most populations. The test consists of three pages, each with four line drawings on it (see Appendix B for plates and word lists). The examiner asks the subject to point to which of the four drawings on a page best illustrates the meaning of a given word. The subject replies by pointing. Testing with a given page continues until there have been six consecutive passes and six consecutive failures, or the end of the stimulus list is reached. All responses are recorded on a record sheet, which lists the items, the correct answers, and the level of difficulty for each item. The subject receives credit for all correct responses, whether or not his/her reasoning is logical. Summary scores, estimated IQs, and percentile ranks are easily computed, or read from tables on the record form.

Published data on the Quick Test suggest that this test shows both reliability and a high degree of correlation with the Wechsler Adult Intelligence Scale (Mednick, 1969; Ogilvie, 1965; Stewart, Cole, & Williams, 1967). Based on these findings, and the fact that the Quick Test is both quick and easy to administer, and intrinsically interesting to patients, the Quick Test was used to estimate the intelligence of the depressed patients in the present study. The

concurrent validity of the Quick Test was assessed by administering the Vocabulary Subtest of the WAIS-R, the subtest most highly correlated with full scale IQ.

Clinical assessment

Clinical assessment of patients in this study involved the use of both diagnostic ratings and assessment of the symptom and severity patterns of the patients' depression.

Diagnostic ratings.

The purpose of the initial diagnostic ratings was to permit reliable selection of a relatively homoegeneous sample of depressed persons for research purposes, without reference to etiology or treatment. The prevalent diagnostic system in the United States, the Diagnostic and Statistical Manual of Mental Disorders ([DSM-III]; American Psychiatric Association, 1980) was used to determine the presence of an actual disorder (or group of disorders) in this sample. The Major Affective Disorders are subdivided into Bipolar Disorder and Major Depression, which are distinguished on the basis of whether or not a manic episode has ever occurred. Bipolar Disorder is subdivided into three groups: currently manic, currently depressed, and mixed (for those who show symptoms of both mania and depression within a single episode). The term "major depression" is used for most unipolar depressions. The DSM-III criteria for major depressive episode are presented in Table 2 (Appendix D). In addition, the current episode was also subclassified on the basis of whether or not melancholia and psychotic features were present. In DSM-III, the term "melancholia" is

similar to the term "endogenous depression", referring to those patients who manifest a particular cluster of vegetative signs and biorhythmical changes, whether or not precipitating events appear to have triggered the depression. Characteristics of this subgroup include loss of pleasure in almost all activities, and at least three of the following: distinct quality of depressed mood, diurnal variation, early morning awakening, significant psychomotor agitation or retardation, significant anorexia or weight loss, and excessive or inappropriate guilt. The diagnosis of psychotic depression was based on whether or not certain psychotic features, such as delusions and hallucinations, were present.

In addition, subjects in this study were classified as having a primary or a secondary depression, on the basis of natural history (Munro, 1966; Robins & Guze, 1972). Primary depression was defined as a major depressive episode occurring in an individual with no prior history of any other nonaffective psychiatric illness. Secondary depression was defined as a depressive episode which occurred subsequent to any nonaffective psychiatric disorders such as alcoholism, anorexia nervosa, anxiety disorders, schizophrenia, mental retardation, organic brain syndrome, drug addiction, etc. The rationale behind this distinction is that the secondary depression would resemble the antecedent disorder in terms of course and prognosis (Woodruff, Murphy, & Herjanic, 1967). More fundamentally, because depression accompanies many mental and physical disorders, it is alleged that "primary" depression is a more "pure" form, a unitary disorder unto itself, and not a mere reactive symptom. The utility of

the primary-secondary classification in research applications is that it permits the definition of more homogeneous groups: patients with primary depression are viewed as unaffected by the numerous psychiatric symptoms and biological phenomena which may accompany other psychiatric disorders.

Patients in the present study are further subdivided on the basis of family history (Winokur, 1979; Winokur, Cadoret, Dorzab, & Baker, 1971). Winokur (1979) has proposed that there are three types of major depression: patients who have a family history of depressive disorder only (pure depressive disease); patients with a family history of alcoholism, antisocial personality, hysteria, or drug abuse, either alone or in combination with depression (depression spectrum disease); and patients with no family history of affective disease (sporadic depressive disease). Patients with a family history of schizophrenia or other psychiatric disorders not listed above were classified as belonging to a fourth group for data coding purposes in the present study. According to Winokur these guidelines define distinct subgroups of patients with different sociodemographic, genetic, and biologic characteristics. For example, a patient with depression spectrum disease was more likely to be a woman with onset of depression before age 40, with a variable course to the depression, and a poor response to tricyclic antidepressants. On the other hand, the typical patient with pure depressive disease was a male with age of onset after 40, showing a good response to tricyclics, but a greater likelihood of relapse. Cross-validation research from the NIMH Collaborative Program on the Psychobiology of Depression found only partial confirmation of

the differences between these subgroups (Andreasen & Winokur, 1979). One study which supported Winokur's system found that 76 per cent of patients with pure depressive disease were DST nonsuppressors, whereas only 7 per cent of patients with depression spectrum disease failed to suppress (Schlesser, Winokur, & Sherman, 1977). In general, considerable validation of this classification system needs to be performed, especially outside of the center in which it was originally developed.

Finally, subjects were classified as having endogenous depression or nonendogenous depression, based on the discriminant function classification system of Feinberg and Carroll (1982). Eight clinical features of depression are used in this system, based on all clinical material available. This includes data derived from administration of the SADS, as well as any information available from clinical interviews, response to treatment, and/or followup. The simplified discriminant function, or discriminant index (all weights rounded to one significant digit), was calculated for each patient to yield an overall rating of endogenicity. In the same study in which Feinberg and Carroll developed this scale, the discriminant index was validated against an objective biological measure, the DST, and found to predict DST status as effectively as clinical diagnosis. The formula for calculating the discriminant index, as well as instuctions for deriving individual clinical feature scores, are presented in Appendix E.

Assessment of depressive symptomatology and severity.

Assessment of the severity of the depressive disorder and of the symptom patterns characterizing each subject's depressive episode were

based on both interview methods (examiner ratings) and patient self-ratings. Copies of these ratings scales are included in Appendix E.

The Hamilton Depression Rating Scale ([HDS]; Hamilton, 1960) provided a profile of the major depressive features present at initial contact with the subject. Hamilton's original scale consisted of 21 items, 17 of which were scored. The version of the HDS used in the present study is based on the 24-item scale currently being used in the NIMH Treatment of Depression Collaborative Research Program (Elkin, Parloff, Hadley, & Autry, 1985). The three additional items assess the "cognitive" symptoms of hopelessness, helplessness, and worthlessness. All items were included in the total score. This modification in scoring has not been found to significantly influence the reliability and validity coefficients of the HDS (Hedlund & Vieweg, 1979; Sotsky & Glass, 1983).

The HDS is one of the most frequently used severity measures, particularly with inpatients. In general, scores of 6 or less are considered to reflect nondepressed functioning; scores of 7-17 reflect mild depression; scores of 18-24 represent moderate depression; and scores of 25 or more reflect severe depression (Sotsky & Glass, 1983). The reliability of HDS ratings has been found to be enhanced when two raters complete the HDS for each interview (Epstein, 1979). Moreover, data on inter-rater reliability are impressive. Hedlund and Vieweg (1979) reviewed nine studies which report inter-rater reliability coefficients of .84 or greater (this includes all available research reports on the HDS from 1967 to 1979). Inter-rater reliability (research associate, senior attending psychiatrist) in the present

study was .94.

In conjunction with the HDS, an overall severity rating was determined for each subject using the Global Assessment Scale (GAS) from the Meninger Foundation Psychotherapy Research Project's Health-Sickness Rating Scale (Waskow & Parloff, 1975). This 100-point scale, broken down into 10-point increments (each with descriptive anchor points), covers a broad array of patient functioning, ranging from grossly impaired in all areas (requiring constant supervision) to superior functioning (asymptomatic). These anchors include overall degree of functional impairment, specific symptoms, quality of interpersonal relationships, and general severity of problems. Interrater reliability, concurrent validity, and predictive validity were assessed by Endicott, Spitzer and colleagues in five studies and reviewed in the initial GAS publication (Endicott, Spitzer, Fleiss, & Cohen, 1976). In general, the precision of ratings was fairly high.

Patient self-assessment instruments consisted of the Beck Depression Inventory ([BDI]; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the Raskin Mood Scale (Raskin, Schulterbrandt, Reatig, & McKeon, 1969). Both scales are standard self-report inventories which have been used extensively in both clinical and research settings. The BDI is the most frequently used self-assessment scale of severity of depression. Each of the items in this 21-item scale consists of four self-evaluative statements, scored 0 to 3. In general, scores in the 0 to 9 range indicate a normal nondepressed state, 10-15 represents mild depression, 16-23 reflects moderate depression, and scores over 24 reflect severe depression. The BDI score correlates well with clinical

judgment (concurrent validity), usually between 0.62 and 0.77 (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Bumberry, Oliver, & McClure, 1978; Strober, Green, & Carlson, 1981). Moreover, correlations of 0.72 to 0.82 with the HDS have been reported (Bech et al., 1975). The Raskin Mood Scale (Raskin, Schulterbrandt, Reatig, & McKeon, 1969) served as an additional subjective measure of the presence and severity of depressive symptoms in the present study. The Raskin is a 52-item adjective check list, gleaned from a variety of sources (e.g., Clyde Mood Scale [Clyde, 1963], Symptom Checklist [Parloff, Kelman, & Frank, 1954], etc.). Each item on the scale is rated on a 4-point intensity scale. An initial factor analytic study on the internal structure of the Raskin (Raskin, Schulterbrandt, Reatig, & Rice, 1967) identified 8 major factors, all of which were consistent with depressive symptomatology or its absence: depressed mood, hostility, guilt and worthlessness, anxiety-tension, fatigue, "carefreeness", cognitive loss, and friendliness. These same factors emerged in a replication of the original study (Raskin, Schulterbrandt, Reatig, & McKeon, 1969) in a sample of 648 depressed patients from 10 hospitals. Further, the loadings of the key items on these factors were highly similar in both studies. Although this scale is not specifically designed to provide a summary score for severity of depression, it does provide "profiles" of scores so that the specifics of symptomatology and mood can be measured, charted, and related to neuroendocrine variables in the present study. This mood scale was one of several included in the NIMH Collaborative Study on the Psychobiology of Depression. Reliability and validity measures for this scale were determined, but have not yet

been published, and are not available at the present time.

Neuroendocrine assessment

Plasma and urinary cortisol determination.

Plasma cortisol was measured with a solid-phase radioimmunoassay kit (Gammacoat Cortisol R.I.A. kit), manufactured by Travenol-Genentech Diagnostics (Cambridge, MA). This radioimmunoassay and the competitive binding principles of radioimmunoassay have been described elsewhere (Travenol-Genentech Diagnostics, 1985; Yalow & Berson, 1971). Following incubation and aspiration, all samples were counted in a gamma counter (Packard Auto-Gamma Scintillation Spectrometer) for one minute, with the window suitably adjusted for iodine-125. Cross-reactivity with other endogenous plasma or urinary corticosteroids (e.g., cortisone, corticosterone, 11-deoxycortisol) totalled less than 15% at 50% inhibition of maximum binding, and was less than 0.1% for dexamethasone. All plasma samples were analyzed in duplicate, using 10 microliter aliquots of the sample. For plasma cortisol, interassay coefficients of variation for medium and low plasma pools (mean 14.7 and 2.2 mcg/dl, respectively), determined from the mean of the average of duplicates for 20 separate runs, were $\pm$9.8% and $\pm$21.1%, respectively. Intrassay coefficients of variation of medium and low pools, determined from the mean of 20 simultaneous assays per sample, were $\pm$6.3% and $\pm$15.9%, respectively. The lower level of sensitivity for this particular kit (the smallest single value which can be distinguished from zero) is approximately 0.24 mcg/dl.

Urinary free cortisol levels were measured in unextracted urine

using a double antibody radioimmunassay kit obtained from Cambridge Medical Technology (Billerica, MA). For UFC level, interassay coefficients of variation for high and low pools (126.5 and 34.4 mcg/dl, respectively) were ±9.4% and ±14,2%, respectively. Intra-assay coefficents of variation were ±7.0% and ±10.4%, respectively. To ensure completeness of urinary specimens, urinary creatinine was determined for each sample, using a Technicon Auto Analyzer. The method employed is a modification of the procedure of Folin and Wu described in the text, Practical Physiological Chemistry, 14th edit (Oser, 1965). The inter- and intra-assay coefficients of variation for creatinine levels are less than 10%. High sensitivity has been obtained using this methodology: in fact, concentrations as low as .05-.10 mg/dl can reliably be distinguished from zero in this laboratory. Urinary creatinine was evaluated in relation to the following criteria for creatinine excretion (Stokes et al., 1984): for women, 14-21 mg/kg of body weight per 24 hours, and for men, 21-28 mg/kg of body weight per 24 hours. If the creatinine level for a 24-hour specimen did not fall within ±20% of these limits for the normative range or if it varied more than 20% on the pre- and post-dexamethasone days, the urine sample was excluded from the analyses.

Plasma ACTH determination.

Plasma ACTH was measured by radioimmunassay using reagents purchased from Radioimmunoassay Systems Laboratories (Carson, California). In order to improve assay sensitivity above that provided by the manufacturer, a double antibody technique was used. The primary ACTH antibodies are obtained from IgG Corporation (Nashville,

Tennessee). The secondary (precipitating) antibody is goat anti-rabbit globulin (Calbiochem, LaJolla, California). This assay uses two 24-hour incubations for maximum sensitivity. ACTH is measured directly, without prior extraction. The primary antibody used in this assay recognizes ACTH 1-24 and ACTH 1-39, but not ACTH 1-13 (alpha-MSH), and thus recognizes the biologically-active species. Cross-reactivity with other POMC-fragments (beta-endorphin, beta-MSH, gamma-MSH, etc.) is essentially zero. The minimum assay sensitivity for ACTH is approximately 15 pg/ml. The respective inter- and intra-assay coefficients of variation are 15% and 10%. To further minimize variability all samples from each patient were determined in one run.

Plasma dexamethasone determination.

In order to assess whether patients had ingested the 1 mg dose of dexamethasone, dexamethasone concentrations were determined on 9 a.m. plasma samples. Plasma dexamethasone was measured by a modification of the RIA method of Meikle et al. (1973), using a double-antibody procedure to increase sensitivity. The first antibody was IgG-Dex-1 obtained from the IgG Corporation (Nashville, TN). Goat anti-rabbit IgG serum served as the second antibody (Calbiochem, LaJolla, CA). Steroid cross-reactivity with the anti-sera used in this RIA was generally less than .01%. The minimal detectable plasma concentration of dexamethasone was 0.1 ng/ml. Thus, this assay is highly sensitive and specific. All patient samples were run in duplicates in one run within the same assay. Maximum interassay and intraassay coefficients of variation were less than 15% and 10%, respectively, as determined by low, medium, and high serum dexamethasone pool replicates placed in

each assay.

## PROCEDURES

Sixty-three patients selected from consecutive admissions to the Payne Whitney Clinic, who satisifed DSM-III criteria for major depression were approached for participation in this study, usually 1-2 days after admission. Before approaching any of the patients, permission to examine the medical case notes and to carry out research procedures was obtained from each patient's primary therapist. All subjects gave oral and written informed consent after we thoroughly described the study procedures. A copy of the consent form used in this study is presented in Appendix F. During this initial semi-structured interview, an HDS and a GAS were completed on each subject by the research associate and senior attending psychiatrist. The research associate and psychiatrist then met for diagnostic conference, where items of information were cross-checked, and an average score was calculated for both of the rating scales.

At 11 a.m. the following day (Study Day 1), the patient was brought to the Laboratory of Psychobiology/Psychoendocrinology for neuropsychological assessment. We selected this time of day because HPA activity is relatively quiesent, thus minimizing the effects of endogenous hormone fluctuations on cognitive performance. Subjects were asked to fill out the BDI and Raskin Mood Scale at this time. Then, an array of neuropsychological tests was administered to each patient, as follows: Vocabulary, Purdue Pegboard, Digit Span, Trail Making Test, Ammons Quick Test, Block Design, and Rey AVLT. The format

and administration of the tests were standardized to allow for appropriate pacing, specific order of presentation, and consistent scoring. This order of presentation minimized carryover effects between different tests and helped maintain subject interest by providing a variety of tasks requiring diverse cognitive abilities. This first testing session usually took 90 minutes to complete. The second part of the battery (Digit Symbol, Babcock, Stroop, Finger-Tapping, Benton VRT, Category Test, and Paced Addition) was administered in a similar manner on the following day (Study Day 2), and usually required 120 minutes for completion.

Neuroendocrine assessments were not performed on the days of neuropsychological testing for three reasons. First, Mason and colleagues (1965) and others have shown that the nonspecific stress of acute hospitalization may in itself produce DST nonsuppression, immediately following admission. A three to four day adjustment period before endocrine evaluation has been found to significantly reduce this likelihood. Second, a review of the literature (vide supra) suggests that exogenous administration of steroids may alter cognitive performance. Third, the results from an earlier pilot study (C. Sikes, unpublished data) on normal controls (using an abbreviated form of this battery) indicated that subjects with test-anxiety may show cortisol non-suppression, even following 8 mg of dexamethasone.

At 11 p.m. on Study Day 2, a 24-hour urine collection for baseline UFC was opened. Procedures for urine collection were explained to the subjects. To assure completeness of urine collection patients were closely monitored by the nursing staff, and all urine losses were

recorded. All voided urine was collected and added to a 1 gallon (3.8 L) plastic container (labelled with the patient's name and date of collection) within an hour of voiding. This container was refrigerated until measurement at the end of 24 hours. When the specimen was completed, it was measured immediately, the date and volume recorded, and a 1.25 ml aliquot of urine saved and frozen at -20°C, until assayed for creatinine and UFC. The remainder of the urine was discarded.

On Study Day 3, venous blood was collected for basal plasma cortisol and ACTH at 9 a.m. and 4 p.m. in chilled ethylenediaminotra-acetate (EDTA [1 mg ml blood]) containing tubes, and immediately placed on ice. The samples were then centrifuged at 4° C at 2500 rpm for 10 minutes for the separation of plasma. Separate aliquots for ACTH and cortisol were stored at -70°C and -20°C, respectively, until assayed. Dexamethasone, 1 mg, was administered orally by a nurse at 11 p.m. The baseline urine collection was closed at 11 p.m., and a second 24-hour collection for post-dex UFC was opened, following the procedures outlined above.

Blood samples for post-dexamethasone ACTH and cortisol were obtained at 9 a.m. and 4 p.m. on Study Day 4, and processed as previously indicated. Plasma cortisol and ACTH, and urinary cortisol were assayed using the commercially available kits, described above. To minimize assay variability, all samples from an individual subject were assayed within a single run. The technicians conducting the assay had no knowledge of the psychiatric or the DST status of the patient.

A criterion of 5 mcg/dL of cortisol or greater at 9 a.m. was used to define DST nonsuppresson (Stokes et al., 1984). The suggested upper

limit of normal for 24-hour UFC using our assay procedures is 100 mcg, which is similar to the upper limit reported by others (Carroll et al., 1976). With our ACTH assay, the normal range of plasma ACTH in the morning is 10-90 pg/ml.

# CHAPTER 3

## RESULTS

The major aim of this study was to explore clinical differences between various biologically distinct subgroups of depressed patients using standardized measures of affective and cognitive functioning as the major dependent variables. Specifically, affective profile and neuropsychological performance were evaluated in terms of various indices of hypothalamic-pituitary-adrenocortical functioning: (1) intactness of feedback mechanisms (reflected in cortisol response to dexamethasone); (2) baseline measures of cortisol and ACTH; and (3) 24-hour urinary free cortisol. Based on previous studies of other groups of patients with HPA disturbances, it was hypothesized that depressed patients who showed similar HPA abnormalities would also demonstrate distinct patterns of neuropsychological impairment that reflected a common underlying neurobiological defect.

Because multiple criterion variables were used, and because the relationships among these variables were of interest, multivariate techniques (particularly multivariate analysis of covariance [MANCOVA] and discriminant function analysis) and univariate correlational analyses formed the core of the analyses. Data management and analyses were performed using the statistical procedures available in SPSS/PC+.

The results of this study are presented as follows: First, the clinical and neuropsychological characteristics of the entire patient sample are described. Next, the findings related to disturbances in feedback inhibition as measured by the DST (i.e., suppressors vs. nonsuppressors) are described. Comparisons of these groups on

demographic, clinical and cognitive variables are then presented. The third major section includes analyses of the relationship between pre-dexamethasone ACTH levels and demographic, clinical, and cognitive variables. In the final major section, analyses of urinary free cortisol data and its relationship to these same variables are presented.

Descriptive data

Clinical characteristics.

Objective measures of the severity of symptomatology indicate that, on the whole, the group was moderately to severely depressed with a high degree of endogenous symptomatology. Average scores on the severity measures used in this study are presented in Table 4.

The mean Global Assessment Score (GAS) of 47.4 indicates that the average patient in this sample was seriously impaired in several areas of everyday functioning. These include work, familial responsibilities, judgment, thinking, mood, communication, and reality testing. The average Hamilton Depression Score (HDS) of 28.6 is consistent with severe depression requiring inpatient hospitalization. The Carroll Endogenicity score of 34.1 reflects a high degree of endogenous symptomatology. Because the distribution of these scores was strikingly normal (unimodal, with means falling at the 50th percentiles of the distributions) these scores appear to accurately describe the majority of subjects in this sample. With respect to the extremes of the distributions, no patients were "unimpaired" on the GAS (i.e., considered able to function outside the hospital), and none fell below

TABLE 4

MEANS, STANDARD DEVIATIONS, AND RANGES

OF OBJECTIVE SYMPTOMATOLOGY MEASURES

| Scale | Mean | SD | Range |
|---|---|---|---|
| GAS | 47.4 | 8.7 | 30 - 70 |
| HDS | 28.6 | 6.3 | 15 - 46 |
| CARROLL | 34.1 | 12.8 | 2 - 59 |

the criterion for moderate depression on the Hamilton. The scores from 76.1% of these patients were above the cutoff for "definitely endogenous" on the Carroll.

Patient self-ratings of depression and mood disturbance are presented in Table 5. The patients' own assessment of the severity of their symptomatology paralleled that of the objective ratings. The average score on the Beck Depression Inventory reflects severe depression (cutoff >24). On the Raskin, self-ratings on the Depression, Anxiety, Fatigue, and perceived Cognitive Loss subscales fell closest to the "Quite a Bit" rating point (score = 3); Hostility, Guilt, and Friendliness fell closest to the "A Little" rating point (score = 2); and Carefreeness closest to "None" (score = 1).

The actual diagnostic characteristics of this sample are presented in Table 6. Three types of diagnostic classifications were used: DSM-

TABLE 5

MEANS, STANDARD DEVIATIONS, AND RANGES OF

SELF-RATINGS OF SYMPTOMATOLOGY & MOOD

| Scale | Mean | SD | Range |
|---|---|---|---|
| Beck | 30.9 | 12.7 | 6 - 60 |
| Raskin: | | | |
| Depression | 2.9 | 0.7 | 1.00 - 4.00 |
| Hostility | 1.9 | 0.7 | 1.00 - 4.00 |
| Guilt | 2.3 | 0.8 | 1.00 - 4.00 |
| Anxiety | 2.6 | 0.7 | 1.17 - 4.00 |
| Carefreeness | 1.3 | 0.4 | 1.00 - 2.33 |
| Fatigue | 2.6 | 0.7 | 1.00 - 4.00 |
| Cognitive Loss | 2.8 | 0.6 | 1.29 - 4.00 |
| Friendliness | 2.3 | 0.7 | 1.00 - 4.00 |

III, a natural history classification, and a system based on the family history of depression or depression spectrum disorders. The breakdown of patients according to DSM-III Axis I (clinical syndromes) indicated that more than three-quarters of the sample presented to the hospital with major depression and no prior history of mania. About half of the sample was assigned concurrent personality disorder diagnoses (Axis II), predominantly involving features from several of the personality disorders without meeting the criteria for any one

TABLE 6

DIAGNOSTIC CHARACTERISTICS OF PATIENTS

| Diagnostic System | # of Patients | % of Patients |
|---|---|---|
| DSM-III (Axis I) | | |
| Unipolar depressed | 48 | 80.0 |
| Bipolar depressed | 10 | 16.7 |
| Mixed | 2 | 3.3 |
| Melancholic | 29 | 48.3 |
| Nonmelancholic | 31 | 51.7 |
| Psychotic | 8 | 13.3 |
| Nonpsychotic | 52 | 86.7 |
| DSM-III (Axis II) | | |
| None | 31 | 51.7 |
| Mixed | 13 | 21.7 |
| Obsessive/compulsive | 1 | 1.7 |
| Borderline | 8 | 13.3 |
| Dependent | 2 | 3.3 |
| Histrionic | 1 | 1.7 |
| Narcissistic | 1 | 1.7 |
| Avoidant | 3 | 5.0 |
| Natural History | | |
| Primary | 51 | 85.0 |
| Secondary | 9 | 15.0 |
| Family History | | |
| Pure depression | 19 | 31.7 |
| Depression spectrum | 8 | 13.3 |
| Sporadic depression | 30 | 50.0 |

specific disorder. These "personality disorder" diagnoses were usually made, however, during acute affective episodes and may only represent situational reactions to the affective disorder itself. About half of

the sample had a DSM-III diagnosis of Melancholia. This accords with the finding of a high average Carroll Endogenicity Scale score. Carroll Endogenicity scores for melancholic patients were markedly and significantly higher than those of nonmelancholic patients (means in this sample = 42.1 and 26.6, respectively; $t$ = 5.73, $df$=56, $p$ <.001), probably as a result of an overlap in criteria for the two scales (shared items for diminished appetite, inappropriate or excessive guilt, psychomotor agitation or retardation, loss of pleasure). Classification of patients based on the DSM-III melancholia criteria and Carroll Endogenicity system was not completely concordant, however, because the former was designed to classify a pattern of behaviors, while the latter was developed to describe specific etiologies of depression. In contrast to the high degree of melancholia/ endogenicity, only a small percentage of the sample had mood-congruent delusions or hallucinations.

Based on the natural history classification, 85% of the sample was characterized as meeting the criteria for major depression without any previous history of nonaffective psychiatric disorder or concurrent incapacitating medical illness (i.e., primary depression). The remaining 15% of patients were classified as having a secondary depression, i.e., having depressive illness which occured subsequent to some other nonaffective psychiatric disorder, such as an anxiety disorder, alcoholism, substance abuse, etc.

Finally according to the family history classification (Winokur-Iowa Classification system), 31.7% of patients in this sample were "familial pure", i.e., had at least one first degree relative with a

major affective disorder. An additional 13.3% had at least one first degree relative with a depression spectrum disorder (alcoholism or sociopathy). Overall, 45% of this sample had some type of familial background (presumptively genetic) for major affective or related disorders.

Neuropsychological characteristics.

Average scores on the neuropsychological tests administered in this study, and the percent of patients whose performance fell below standard criteria for "impairment" (suggestive of brain damage or dysfunction) are presented in Table 7.

The average estimated IQ of 107.4 (based on Ammons Quick Test performance) for the sample falls within the average range of the general population, approximately one-half standard deviation above the mean. This estimate of IQ was corroborated by performance on the Vocabulary subtest, the WAIS-R subtest which is most highly correlated with overall IQ. Vocabulary scores were correlated .89 with Ammons IQ, and the mean Vocabulary score was consistent with an IQ from 105 to 110. Mean scores on the other WAIS-R tasks included in this study (Digit Span, Digit Symbol, Block Design) also fell within the range of estimated IQ. Rates of impairment on these subtests were less than 10%. Scores on other measures fell further below this level of performance. On the Stroop Color-Word Test, mean T-scores for color and color-of-word identification were approximately one standard deviation below the standardization sample mean (for T-scores, 50 $\pm$ 10 by convention). Fifty percent or more of the sample was impaired on each of these tasks. On the Babcock Story Recall, over 60%

TABLE 7

NEUROPSYCHOLOGICAL TEST SCORES

| Neuropsychological Test | Average Score | % Impaired |
|---|---|---|
| Ammons Quick Test (IQ) | 107.4 ± 14.0 | -- |
| WAIS-R Vocabulary | 11.9 ± 3.1 | -- |
| WAIS-R Digit Span | | |
| Forward (Raw) | 8.3 ± 2.5 | 8.3 |
| Backward (Raw) | 6.6 ± 2.7 | 6.7 |
| Stroop Color-Word | | |
| Word | 45.6 ± 8.8 | 20.0 |
| Color | 38.4 ± 9.4 | 60.0 |
| Color-Word | 40.9 ± 10.7 | 50.0 |
| Interference | 48.0 ± 7.9 | 16.7 |
| Babcock Story Recall | | |
| Immediate | 11.6 ± 3.8 | 61.7 |
| Delayed | 11.2 ± 4.9 | 68.3 |
| Rey AVLT | | |
| Trial 1 | 5.7 ± 1.6 | 11.7 |
| Trial 5 | 10.5 ± 2.9 | 5.0 |
| Trial 7 (Recall) | 8.0 ± 3.4 | 18.3 |
| Recognition | 11.7 ± 3.5 | 20.0 |
| Benton VRT | | |
| Admin A: # Correct | 5.9 ± 2.2 | 18.3 |
| # Errors | 6.4 ± 4.3 | 36.7 |
| Admin D: # Correct | 5.3 ± 2.6 | 36.7 |
| # Errors | 8.0 ± 5.6 | 51.7 |
| Finger Tapping | | |
| Dominant Hand | 43.6 ± 11.6 | 40.0 |
| Nondominant Hand | 39.9 ± 9.7 | 33.3 |
| Purdue Pegboard | | |
| Dominant Hand | 12.7 ± 2.7 | 30.0 |
| Nondominant Hand | 11.7 ± 2.8 | 26.7 |
| Both Hands | 9.8 ± 2.5 | 35.0 |
| WAIS-R Digit Symbol | 10.0 ± 3.1 | 5.0 |
| Trail Making Test | | |
| Part A (Time in Sec) | 48.1 ± 42.7 | 21.7 |
| Part B (Time in Sec) | 117.4 ± 79.7 | 25.0 |
| WAIS-R Block Design | 9.7 ± 2.5 | 1.7 |
| Category Test | 51.6 ± 29.7 | 46.7 |
| Paced Serial Addn (n=49) | | |
| Admin A | 31.2 ± 16.7 | 65.3 |
| Admin B | 30.6 ± 15.9 | 53.1 |

of subjects were impaired on both portions of the test. Performance on the Rey Auditory Verbal Learning Test was slightly better, with patients performing at the low end of the normal range, but on all remaining tasks, 25% to 50% of subjects were performing within the impaired range on some portion of each test. Because a number of subjects had difficulty completing the Paced Auditory Serial Addition Test according to instructions, and because a complete score was not obtained from 10 patients due to their complaints about its difficulty, this test was dropped from subsequent statistical analyses.

Overall, subjects were impaired on an average of 7.4 ($\pm$ 4.3) of 26 neuropsychological measures obtained (exclusive of IQ estimation measures and Paced Addition). These impairments were reflective of a nonspecific decrement in performance, with no unique functional impairment (e.g. motor, memory, concentration) or focal findings evident in the total sample.

Endocrine measures.

Endocrine measurements were made on the day of, and the day following an 11 p.m. administration of 1 mg dexamethasone. Plasma cortisol and ACTH were assessed at 9 a.m. and 4 p.m. on each day. Urinary free cortisol, an integrated 24-hour measure, was assessed over the course of each 24-hour period. The means ($\pm$ s.d.), medians, and ranges of each measure are presented in Table 8.

For the entire sample, mean plasma cortisol levels on the pre-dexamethasone day were within the high normal range. The upper limits of normal are defined as approximately 20 mcg/dl for a.m., and 12

TABLE 8

MEANS, STANDARD DEVIATIONS, MEDIANS, AND RANGES OF ENDOCRINE MEASURES

| Measure | Mean ± s.d. | Median | Range |
|---|---|---|---|
| Plasma Cortisol: | | | |
| Pre-Dexamethasone a.m. | 18.6 ± 8.0 | 15.4 | 9.4 - 48.7 |
| Pre-Dexamethasone p.m. | 11.8 ± 6.4 | 10.3 | 4.5 - 40.0 |
| Post-Dexamethasone a.m. | 6.9 ± 8.2 | 2.4 | .7 - 46.0 |
| Post-Dexamethasone p.m. | 6.9 ± 7.4 | 4.1 | .7 - 44.6 |
| Plasma ACTH: | | | |
| Pre-Dexamethasone a.m. | 61.1 ± 32.6 | 60.0 | 18 - 194 |
| Pre-Dexamethasone p.m. | 52.9 ± 28.0 | 48.0 | 14 - 138 |
| Post-Dexamethasone a.m. | 45.0 ± 27.5 | 38.0 | 13 - 126 |
| Post-Dexamethasone p.m. | 43.4 ± 23.3 | 40.0 | 13 - 114 |
| Urinary Free Cortisol: | | | |
| Pre-Dexamethasone | 123.3 ± 59.3 | 101.2 | 38.1 - 286.5 |
| Post-Dexamethasone | 52.7 ± 44.1 | 33.5 | 7.8 - 185.4 |

mcg/dl for p.m. plasma cortisol. The distribution of these values, however, was positively skewed: medians fell below the means and the range extended over 3.5 standard deviations above the mean. The extreme (highest) value in the distribution of each of the plasma cortisol measures, pre-and post-dexamethasone, was represented by the same patient. This patient was treated as an outlier in all subsequent comparisons where plasma cortisol was analyzed as a continuous variable.

On the pre-dexamethasone day, plasma cortisol decreased significantly from morning to afternoon (paired $t$=8.75, $df$=59, $p$<.001).

Post-dexamethasone cortisols were each significantly lower than either of the basal (pre-dexamethasone) values (pre a.m/post a.m. comparison, $t$=11.99, $df$=59, $p$<001; pre p.m./post p.m., $t$=6.86, $df$=58, $p$<.001; pre p.m./post a.m., $t$=5.30, $df$=59, $p$<.001). Morning and afternoon cortisols were not significantly different on the post-dexamethasone day ($t$=0.13, $df$=58, $p$=.893). As expected, dexamethasone suppresses both the absolute level of cortisol output and the usual pattern of diurnal variation on the day after administration.

Similar to the cortisol data, mean ACTH values on the pre-dexamethasone day fell within a normal range (upper limit approximately 100 pg/ml) and were distributed in a positively skewed fashion. No single case, however, stood out as an outlier.

Post-dexamethasone ACTH values and their a.m to p.m. diurnal variation were also suppressed by dexamethasone. Basal ACTH values differed from morning to afternoon ($t$=4.83, $df$=58, $p$<.001), and were greater than post-dexamethasone ACTH values (pre a.m/post a.m. comparison, $t$=7.66, $df$=59, $p$<001; pre p.m./post p.m., $t$=5.88, $df$=57, $p$<.001; pre p.m./post a.m., $t$=5.01, $df$=58, $p$<.001); post-dexamethasone ACTH values did not differ from a.m. to p.m. ($t$=1.41, $df$=58, $p$<.165).

Mean urinary free cortisols fell within a normal range in a positively skewed distribution. However, a number of UFC samples were excluded, reducing the samples on which these means were based. Fourteen pre-dexamethasone and 22 post-dexamethasone UFC values were excluded because an assay of 24-hour creatinine excretion taken from the same urine sample indicated that patients did not comply with the collection regimen for the full 24-hours. Nonetheless, the

distribution of the complete urinary free cortisol values was comparable to that of the plasma cortisols in overall magnitude and shape. Urinary free cortisols also declined significantly after the administration of dexamethasone ($t$=12.88, $df$=34, $p$<=.001).

In general, the distributions of these endocrine measures suggested that collection and assay procedures were valid, in terms of producing reasonable values for each assessment. The expected suppression of each measure by dexamethasone was observed. The skewness of each distribution indicates that the majority of patients fell within a normal range while a subset had clearly supranormal values.

Suppressor vs. nonsuppressor comparisons

Composition of groups.

Based on a criterion of 5.0 mcg/dl of cortisol at 0900 on the post-dexamethasone day, 37 patients (61.7%) were classified as DST suppressors and 23 (38.3%) were classified as DST nonsuppressors. Selected demographic and clinical characteristics of these two groups are presented in Table 9.

Suppressors and nonsuppressors differed in age, functional impairment (GAS rating), endogenicity of depression (Carroll), and self-rating (Beck) of severity of depression. They differed as well in the percentage of patients diagnosed as psychotic: 7 of 8 patients classified as psychotically depressed were nonsuppressors. Suppressors and nonsuppressors were equivalent, however, on all other

TABLE 9

COMPARISON OF SUPPRESSOR & NONSUPPRESSOR GROUPS

ON SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

| Variable | Suppressors | Nonsuppressors | p |
|---|---|---|---|
| Age | 44.7 ± 16.7 | 59.9 ± 13.6 | .001 |
| Sex (% female) | 83.8% | 65.2% | NS |
| Education | 13.5 ± 3.3 | 13.1 ± 3.1 | NS |
| Est. IQ | 107.2 ± 14.2 | 107.6 ± 14.0 | NS |
| WAIS-R Vocab. | 11.8 ± 3.3 | 12.1 ± 2.9 | NS |
| GAS | 50.7 ± 8.0 | 42.3 ± 7.5 | <.001 |
| HDRS | 27.4 ± 6.7 | 30.3 ± 5.2 | NS |
| Carroll | 29.8 ± 11.9 | 41.6 ± 10.9 | <.001 |
| Beck | 27.4 ± 11.5 | 36.5 ± 12.9 | .007 |
| Bipolar Disorder | 21.6% | 17.3% | NS |
| Melancholia | 37.8% | 60.9% | NS |
| Psychoticism | 2.7% | 30.4% | .007 |
| Axis II Disorder | 56.8% | 34.8% | NS |

demographic, clinical, and diagnostic variables.

The difference in age between suppressors and nonsuppressors is predictable on the basis of prior research. Differences in ratings of functional status (GAS), endogenicity (Carroll), perceived severity of depression (Beck), and psychoticism in the absence of a difference in Hamilton Depression score (HDRS) are notable because nonsuppresors

appear to be more functionally debilitated, endogenously symptomatic, subjectively depressed and psychotic without appearing any more severely depressed overall.

Comparison of overall degree of neuropsychological impairment.

Adjusting for their differences in age, suppressors and nonsuppressors differed in the overall number of neuropsychological tests on which each subject performed within the impaired range. Suppressors were impaired on an average of 5.8 $\pm$ 3.0 tests, whereas nonsuppressors were impaired on 10.1 $\pm$ 4.7 tests ($F$=11.13, $df$=1,57, $p$=.002). Age, as expected, was found to covary significantly with the overall number of impaired scores ($F$=12.87, $df$=1,57, $p$=.001).

Approach to comparison of performance on individual neuropsychological measures.

The performance of suppressor and nonsuppressor groups on individual neuropsychological measures was compared next. Because multiple measures of performance were employed in this study, a multivariate analysis of variance approach was used. Differences in age between the groups necessitated its inclusion as a covariate, to adjust for the effect of age on neuropsychological test scores. Thus, a multivariate analysis of covariance (MANCOVA) was the actual statistical technique employed. A priori differences between the groups in functional impairment and depression severity measures were not treated as covariates for the following reasons: the functional impairment (GAS) rating was treated as synonymous with the neuropsychological tests - the two rate the same things in less vs. more specific ways. Similarly, the endogenicity (Carroll) rating was

designed to be consistent with DST results, and thus was confounded with the independent variable. Degree of subjective depression (Beck) was not used as a covariate because it was found to be uncorrelated with neuropsychological performance in this sample.

The a priori group difference in psychoticism suggested that those patients diagnosed as psychotic should be analyzed separately. However, within the nonsuppressor group, psychotic patients were no different than non-psychotic patients in terms of any measures of clinical severity (GAS, Hamilton, Carroll, and Beck) or neuropsychological performance. Because they were representative of the larger group of nonsuppressors, a separate analysis of these patients was not performed.

Due to the large number of dependent measures obtained in this study, the following steps were taken to insure appropriate application of multivariate statistical procedures. First, the number of dependent measures was reduced from 26 to 12 by either (a) adding highly corrrelated measures from the same test to obtain a single measure which represented total test variability (c.f. Bray and Maxwell, 1985 for discussion of this approach), or (b) selecting that single measure from a test which was most important for evaluating the cognitive function the test is purported to measure. Following this variable reduction step, the multivariate analysis of covariance was performed on these variables. Univariate analyses were then conducted on each of the variables included in the overall analysis in order to pinpoint specific differences in functioning between suppressors and nonsuppressors. Following these univariate analyses on variables from

the reduced variable set, the components of significantly different combined scores were analyzed, to better define the nature of group differences on specific measures. Finally, a discriminant function analysis was performed in order to find that subset of tests which best characterized differences between the two groups.

Raw scores, uncorrected for age, were used in multivariate comparisons. Standardized age corrections, which would have eliminated the necessity of covarying for age, were not available for all tests.

Preparation of variable set.

In the variable reduction step, subscores from five neuropsychological tests (WAIS-R Digit Span, Finger Tapping, Purdue Pegboard, Babcock Story Recall, and Benton Visual Retention Test [error scores]) were added to yield a single measure for each test. All combined scores were correlated at least .85 with other measures from the same test and were deemed acceptably representative for inclusion. For the Rey Auditory Verbal Learning Test, a commonly used measure of "Learning" (Trial 5 minus Trial 1 [Lezak, 1983]) was calculated and employed as the single score from this test, since it best defined what the test is purported to measure. Similarly, the estimated Interference score from the Stroop Color/Word Test was selected for inclusion in the multivariate analysis, since the test was included in this study as a measure of susceptibility to attentional interference. At the end of this process, the neuropsych test data set was reduced to the following 12 variables:

WAIS-R Digit Span, Total Digits
Stroop Estimated Interference Score
Babcock Story Recall, Total Immediate & Delayed
Rey AVLT Learning Score

Benton VRT, Total Errors, Admin A & D
Finger Tapping, Total Taps, Each Hand
Purdue Pegboard, Total Placements, Each Hand & Both
WAIS-R Digit Symbol
Trail Making, Part A
Trail Making, Part B
WAIS-R Block Design
Category Test

The measures used to estimate the IQ of individuals in this sample (Ammons, WAIS-R Vocabulary) were not included in the reduced variable set since their purpose in the present study was to ensure the equateability of groups. Neither the Ammons Quick Test IQ estimate, nor the age-corrected WAIS-R Vocabulary score differed between the groups. If these IQ estimates had differed, they would have been used as covariates, not treated as dependent variables. To reduce the potential influence of outliers, the distributions of these variables were examined for skewness and extreme scores. All were approximately normal in shape, with the exception of the Trail Making scores, which were positively skewed. A reciprocal transformation was performed on these scores to normalize their shape and to reduce the influence of extreme outlying scores (commonly obtained on tests where time of execution of the task is the measure of interest). Following this transformation, the variables comprising the reduced variable set were found to have equivalent covariance matrices within each group using a test which is sensitive to departures from multivariate normality (Box's M=127.6, $F$=1.03, $df$=91,6940, $p$=.386).

Multivariate analysis.

The multivariate analysis of covariance revealed significant effects for both the covariate, age (Wilk's Lambda=.454, equivalent $F$=4.61, $df$=12,46, $p$<.001), and the independent variable, dexamethasone

suppression status (Wilk's Lambda=.581, equivalent $F$=2.76, $df$=12,46, $p$=.007). Although neuropsychological performance covaried significantly with age, differences in performance due to suppressor status occured independently of this age effect.

Given the significant overall MANCOVA, univariate tests of significance were performed on the variables included in the overall analysis. The outcome of these comparisons are presented in Table 10. Note that raw (not age-scaled) scores are presented because the univariate analyses of covariance (ANCOVA) adjust these scores for differences in age.

"Protected" $F$-tests on these variables revealed significant ($p$<.05) differences for 6 variables: the Rey Learning score, Benton total errors, the Purdue Pegboard total, Trails B time, WAIS-R Block Design, and the Category Test.

Because three of these significantly different variables were composites, other scores from the same tests were analyzed in order to determine the nature of the group difference on the composite score.

On the Rey, an analysis of Trials 1 and 5, the Immediate Recall Trial, and the Recognition Trial revealed significant age-adjusted differences on all but Trial 1 ($F$=1.66, $df$=1,57, $p$=.203). Significant differences on Trial 5 ($F$=10.48, $df$=1,57, $p$=.002), Recall ($F$=6.83, $df$=1,57, $p$=.011), and Recognition ($F$=7.21, $df$=1,53, $p$=.010) suggested that "learning" is, in fact, the critical difference between the groups. Although the groups were not different after the first trial, nonsuppressors performed consistently more poorly on subsequent trials.

TABLE 10

POST-HOC UNIVARIATE COMPARISONS OF NEUROPSYCHOLOGICAL PERFORMANCE IN DST SUPPRESSORS VS. NONSUPPRESSORS

| Test | Suppressor Mean | Nonsupppressor Mean | F after age adjustment (df=1,57) | p |
|---|---|---|---|---|
| Digit Span Total | 15.5 ± 4.4 | 14.0 ± 5.0 | 1.82 | .182 |
| Stroop Interference | 2.8 ± 8.6 | 4.7 ± 5.4 | 0.00 | .952 |
| Rey Learning | 5.8 ± 2.2 | 3.3 ± 2.4 | 7.74 | .007 * |
| Babcock Recall Total | 24.1 ± 7.5 | 20.7 ± 8.7 | 0.00 | .964 |
| Benton A & D Total Errors | 11.0 ± 6.6 | 21.7 ± 11.7 | 8.41 | .005 * |
| Finger Tap Total | 89.2 ± 14.5 | 74.5 ± 24.8 | 3.30 | .074 |
| Pegboard Total | 37.4 ± 5.8 | 29.1 ± 7.2 | 9.82 | .003 * |
| Digit Symbol | 51.6 ± 14.9 | 38.0 ± 16.8 | 1.69 | .199 |
| Trails A Time (sec) | 35.7 ± 11.9 | 68.0 ± 63.0 | 2.38 | .128 |
| Trails B Time (sec) | 80.4 ± 34.4 | 176.8 ± 95.3 | 4.74 | .034 * |
| Block Design | 27.8 ± 8.9 | 17.7 ± 8.3 | 7.88 | .007 * |
| Category Test Errors | 38.8 ± 26.0 | 72.0 ± 23.4 | 12.45 | .001 * |

*p<.05

On the Benton, analyses of suppressor/nonsuppressor differences in error scores on Administration A vs. Administration D indicated a marginal age-adjusted difference on Administration A ($F$=3.25, $df$=1,57, $p$=.077) and a significant difference on Administration D ($F$=12.30, $df$=1,57, $p$=.001). Group differences appeared more clearly on the more difficult 15-second delayed recall administration.

Finally, scores on the Purdue Pegboard for the dominant, nondominant, and both hands were analyzed. All scores were significantly different (dominant hand $F$=5.09, $df$=1,57, $p$=.028; nondominant hand $F$=9.90, $df$=1,57, $p$=.003; both hands $F$=8.87, $df$=1,57, $p$=.004). Although the dominant hand score was less clearly different than the nondominant and both hands scores, there was no evidence for any lateralized differences.

Differences between suppressors and nonsuppressors, then, appeared to be due to poorer performance by the nonsuppressors on tests of verbal learning (Rey), visual retention (Benton), fine motor coordination (Purdue Pegboard), sequential reasoning (Trails B), visual-spatial organization and reasoning (Block Design), and logical reasoning (Category Test). Consistent differences were not observed on tests of simple motor speed (Finger Tapping), psychomotor speed (Digit Symbol) or simple sequencing (Trails A), attention (Digit Span) or attentional interference (Stroop), or narrative memory (Babcock).

Discriminant function analysis.

In order to identify the set of neuropsychological variables which best characterized the difference between the suppressor and nonsuppressor groups, a stepwise discriminant analysis was performed on

those variables which had been found to differ significantly between the groups (Klecka, 1980).

The following six variables were entered into the stepwise procedure: the Rey Learning score, the Benton Error score from Administration D (because this score appeared to account for the difference obtained in the multivariate post-hoc procedure on total error score), the total of the three Purdue Pegboard trials, Trails B, Block Design, and the Category Test score. Using an F-to-enter criterion of 1.00, and minimizing Wilk's Lambda, the analysis was completed in five steps. The final function included three variables: Rey Learning, Purdue Pegs Total, and the Category Test. Five steps were needed because the Benton Administration D error score was entered on the first and removed on the last step. The following function was obtained:

.2156(Rey Learning) + .0704(Purdue Pegs Total) - .0242(Category Test Errors) - 2.2073 = Discriminant Score.

Following derivation of the discriminant function, a classification analysis was performed to test the accuracy of this function. A summary of the subjects' actual group membership (suppressor, nonsuppressor) versus predicted group membership is presented in the confusion matrix shown in Table 11.

Scores derived from this function correctly classified 83.8% of suppressors, 73.9% of nonsuppressors, and 80.0% of subjects overall

TABLE 11

PREDICTED VERSUS ACTUAL GROUP MEMBERSHIP

FOR DST SUPPRESSORS AND NONSUPPRESSORS

| Predicted group | n= | Actual group: Suppressors | Actual group: Nonsuppressors |
|---|---|---|---|
| Suppressors | 37 | 31 (83.8%) | 6 (16.2%) |
| Nonsuppressors | 23 | 6 (26.1%) | 17 (73.9%) |

(Yate's corrected Chi-Square on this classification = 17.61, $p<.001$). Another indicator of the effectiveness of the discriminant function is the difference between actual discriminant scores within the groups. In an analysis of variance on these scores, the ratio of the between-groups sum of squares to the within-groups sum of squares should be maximized in the derived discriminant function (Klecka, 1980). Table 12 presents the results of the analysis of variance using the discriminant scores as the dependent variable and suppressor status as the classification variable. The eigenvalue (between-groups ss/ within groups ss) for this function was .9214, indicating that the combination of the three predictor variables was very effective in predicting suppressor status.

The purpose of this discriminant analysis, however, was not to generate predictions of suppressor status, but to find a more parsimonious subset of variables which best characterized the

TABLE 12

ANALYSIS OF VARIANCE TABLE FOR DISCRIMINANT SCORE

| Source | Sum of Squares | df | Mean Square | F | p |
|---|---|---|---|---|---|
| Between groups | 53.44 | 1 | 53.44 | 53.44 | .0000 |
| Within groups | 58.00 | 58 | 1.00 | | |

neuropsychological differences between the two groups. Thus, importance was assigned to those variables which remained in the equation after stepwise analysis, and to their relative standardized canonical coefficients.

The standardized canonical discriminant functions indicated that the Category Test score was weighted most heavily (-.6070) in the derived function, with Rey Learning (.4914) and Purdue Pegboard (.4504) weighted slightly less. In terms of what these test are purported to measure, reasoning skill was weighted most heavily in characterizing the difference between suppressors and nonsuppressors, followed by learning ability and fine motor control.

In summary, subjects who were DST nonsuppressors showed more severe cognitive dysfunction than DST suppressors. The nature of this cognitive dysfunction was such that reasoning skills, verbal learning ability, fine motor control, visual memory (delayed), visual-spatial organization, and sequential reasoning were impaired. The essence of the impairment in nonsuppressors appeared to be related primarily to deficits within the first three of these areas.

Predicting degree of impairment in nonsuppressors.

The relationship between neuropsychological performance and the degree of neuroendocrine dysregulation was examined next. DST nonsuppression was defined by a post-dexamethasone a.m. plasma cortisol of 5 mcg/dl or greater, although the cortisol values for some subjects ranged as high as 46 mcg/dl. In order to examine the possible relationship between the elevation of post-dexamethasone cortisol and decrements in neuropsychological performance, correlations between the two sets of variables were performed within the nonsuppressor group. Because the single subject with the highest post-dexamethasone value (46.0) was nearly 3 standard deviations above the next highest value (23.6), and because this outlying subject also had a number of neuropsychological test scores which were near floor values on some tests, correlations are reported both with and without this subject included. Correlations are presented in Table 13. Within the total nonsuppressor group, significant correlations with post-dexamethasone a.m. plasma cortisol level were observed with the Babcock Story Recall total recall (immediate plus delayed administration), the Benton total error score (administrations A plus D), and total Finger Tapping. When the single outlier was removed from the analysis, however, none of these correlations were statistically significant. Apparently, beyond a certain extreme threshold, post-dexamethasone plasma cortisol values are predictive of marked neuropsychological impairment. The subject with the extreme outlying cortisol value was impaired on 17 of the 26 measures administered. Within a more densely distributed range of

TABLE 13

CORRELATIONS BETWEEN NEUROPSYCHOLOGICAL PERFORMANCE AND POST-DEXAMETHASONE AM CORTISOL LEVELS IN DST NONSUPPRESSORS

| Test | Correlation Coefficients (r) Full Sample (n=23) | Outlier Removed (n=22) |
|---|---|---|
| Digit Span Total | -.07 | -.05 |
| Stroop Interference | -.16 | -.22 |
| Rey Learning | -.32 | -.14 |
| Babcock Recall Total | -.55 * | -.26 |
| Benton A & D Total Errors | .48 * | .28 |
| Finger Tap Total | -.59 * | -.14 |
| Pegboard Total | .21 | .28 |
| Digit Symbol | -.23 | -.03 |
| Trails A Time (sec) | -.17 | -.23 |
| Trails B Time (sec) | .05 | .07 |
| Block Design | -.15 | -.23 |
| Category Test Errors | .34 | -.03 |

* $p<.05$

values near the suppression/nonsuppression threshold, however, post-dexamethasone cortisol value per se was not predictive of the degree of neuropsychological dysfunction in nonsuppressors.

General relationship of age and cortisol level.

The marked difference in age between suppressors and nonsuppressors indicated that there was a correlative relationship between age and post-dexamethasone plasma cortisol levels. Such a relationship between a.m. post-dexamethasone cortisol level and age raises questions, however, about a relationship between age and basal plasma measures of cortisol. In order to explore this possibility, age correlations with all plasma cortisol measures obtained in this study were examined. Because one subject had cortisol values which were outliers in every distribution, correlations were computed both with and without this subject included. These correlations between age and cortisol values are presented in Table 14.

Significant correlations between age and cortisol were found with post-dexamethasone values only. Correlations with baseline values (pre-dexamethasone) did not reach the criterion for statistical significance. Removal of the outlier had little effect on the magnitude of correlations, suggesting that these correlations were not merely the result of outlier effects. Generally, these correlations suggest that age affects the reactivity of the hypothalamic-pituitary-adrenal system to provocative testing rather than the output of the system at a single point in time.

TABLE 14

CORRELATIONS BETWEEN AGE AND CORTISOL VALUES

| Test | Correlation Coefficients (r) Full Sample (n=60) | Outlier Removed (n=59) |
|---|---|---|
| Pre-Dexamethasone Cortisol Level (a.m.) | .23 | .21 |
| Pre-Dexamethasone Cortisol Level (p.m.) | .23 | .21 |
| Post-Dexamethasone Cortisol Level (a.m.) | .33 * | .34 * |
| Post-Dexamethasone Cortisol Level (p.m.) (n's=59 and 58) | .28 * | .29 * |

* $p<.05$

Supplemental Analyses.

Self-ratings of mood disturbance.

The more severe cognitive impairment in nonsuppressors was accompanied by higher self-reported ratings of depression on the Beck Depression Inventory, despite non-significant differences in an "objective" rating of the severity of their depression (the Hamilton Depression Rating Scale). The Raskin Mood Scale offered an additional measure of subjects' self-ratings of mood. A multivariate analysis of variance on the eight Raskin mood rating dimensions, with suppressor

status as the independent variable, revealed a significant overall difference between the two groups (Wilk's Lambda=.714, approximate $F$=2.55, $df$=8,51, $p$=.020). Post-hoc univariate analyses of variance were significant for higher self-ratings of Fatigue ($F$=9.38, $df$=1,58, $p$=.003) and Depression ($F$=4.40, $df$=1,58, $p$=.040) in the nonsuppressor group, and approached significance for higher self-ratings of Anxiety ($F$=3.98, $df$=1,58, $p$=.051). The groups did not differ, however, in their ratings of perceived Cognitive Loss ($F$=2.80, $df$=1,58, $p$=.100), or any of the other mood dimensions.

Taken together with the Beck Depression Inventory Scores, the scores of nonsuppressors on the Raskin Fatigue, Depression, and Anxiety dimensions corroborate the finding of a greater subjective sense of depression in this group.

Differential treatment.

Two variables related to treatment received by subjects after their participation in this study (type of treatment and length of hospitalization) were then examined. Suppressors and nonsuppressors were found to differ in the type of treatment received: whereas only 8.1% of supressors received electroconvulsive therapy (ECT), 43.5% of nonsupressors received this treatment (Chi-Square=11.49, $df$=2, $p$=.003). The large majority of suppressors received medication treatment (83.8%) or no treatment (8.1%); nonsuppressors who did not receive ECT received medication (56.5%). In addition to these differing treatments, suppressors were found to have spent less time in the hospital than nonsuppressors. The median hospital stay for suppressors was 29 days, whereas the median stay for nonsuppressors was 36 days (Mann-Whitney

U=248.5, p=.007; [a non-parametric test was used due to highly skewed distributions within each group]). This difference in length of hospital stay was independent of treatment: median length of stay for nonsuppressors was 36 days whether they received ECT or medication (Mann-Whitney U=55.5, p=.555).

Natural and family history of psychiatric disorder.

Two measures of each subject's natural (personal) history of depressive disorder were evaluated in this study. The first was a tally of each patient's previous psychiatric admissions (this was generally relayed by the patient; when the patient was not a reliable historian, this information was obtained from a significant other). I hypothesized that patients with a putative "biological" type of depression (i.e., nonsuppressors), might be expected to have had more frequent episodes of severe depression requiring treatment over their lifetimes. In actuality, the number of previous admissions in both groups was virtually identical (1.38 $\pm$ 1.7 for suppressors and 1.43 $\pm$ 2.0 for nonsuppressors, t=.12, df=58, p=.908). A second measure relating to natural history was the primary/secondary classification, e.g., whether or not depression was the first and most significant psychiatric illness during a patient's lifetime. Nonsuppressors were expected to have a higher proportion of primary depressives, but were found to be no different than suppressors in terms of this percentage (86.5% primary depressions in suppressor group vs. 82.6% in nonsuppressor group; [Yate's Corrected Chi-Square=.17, df=1, p=.970]).

The familial history measure employed in this study is a putative indicator of genetic predisposition to affective or affective spectrum

illnesses (Winokur's classification). The breakdown of suppressors and nonsuppressors according to the Family History Classification is presented in Table 15. Suppressors did not differ from nonsuppressors

TABLE 15

FAMILY HISTORY OF SUPPRESSORS VS. NONSUPPRESSORS

| DST Status | Pure Depression | Depression Spectrum | Sporadic Depression | Misc. |
|---|---|---|---|---|
| Suppressors | 13 | 5 | 16 | 3 |
| (%) | (35.1) | (13.5) | (43.2) | (8.1) |
| Nonsuppressors | 6 | 3 | 14 | 0 |
| (%) | (26.1) | (13.0) | (60.9) | ( 0 ) |

in terms of family history of affective disease (Chi-square = 3.12, $df$=3, $p$=.374). In each group, the largest proportion of patients were classified as having sporadic depression, the next largest group as familial pure, and the remainder as depression spectrum or other.

Relationships with basal cortisol measures.

Basal cortisol and suppressor status.

Basal plasma cortisol measures, obtained in the morning and late afternoon of the predexamethasone day offered an additional means of predicting clinical severity and neuropsychological performance. Suppressors and nonsuppressors differed on these two basal cortisol measures (a.m. means=16.5 $\pm$ 7.0 and 21.9 $\pm$ 8.7, respectively, $t$=2.63,

df=58, p=.011; p.m. means=10.3 ± 5.2 and 14.1 ± 7.5, t=2.29, df=58, p=.026), and each was correlated with absolute value of a.m. postdexamethasone cortisol (r=.57 with a.m., p<.001; r=.55 with p.m., p<.001). Thus, basal cortisol was moderately predictive of cortisol response to administered dexamethasone, with nonsuppressors being more likely to show elevated basal levels.

Morning (a.m.) and evening (p.m.) basal cortisol measures were correlated .67 (p<.001) with each other.

Basal cortisol measures and demographic/clinical data.

Correlations between basal cortisol measures and selected demographic and clinical measures are presented in Table 16. The

TABLE 16

CORRELATIONS BETWEEN BASAL PLASMA CORTISOL MEASURES AND SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

| Variable | A.M. | P.M. |
|---|---|---|
| Age | .23 | .23 |
| Education | .01 | .09 |
| Est. IQ | .00 | .04 |
| WAIS-R Vocab. | -.06 | .00 |
| GAS | -.14 | -.11 |
| HDRS | -.07 | .04 |
| Carroll | .07 | .14 |
| Beck | .13 | .09 |

None significant at p<.05

correlation between these measures and age is discussed above, but is presented here again in context of other demographic relationships. Overall, basal cortisol measures were not significantly correlated with either age, education, estimates of IQ, or depression severity measures.

Basal cortisol measures and neuropsychological functioning.

Correlations between basal cortisol measures and neuropsychological test scores are presented in Table 17. Significant correlations were observed between a.m. predexamethasone cortisol and Babcock immediate recall, number correct scores on Benton Administrations A and D, Finger Tapping (both hands), WAIS-R Block Design, and the Category Test. Significant correlations were also noted between p.m. predexamethasone cortisol and the number correct score for Benton Administration A, both the number correct and number of errors on Administration D, and Finger Tapping (both hands). Given these correlations, predexamethasone cortisol levels appeared to predict a number of the neuropsychological deficits observed among those with elevated postdexamethasone cortisol levels.

The correlations presented in Table 17, however, include the outlier who had been removed from previous correlational analyses involving continuous cortisol measures (vide supra). Correlations between predexamethasone cortisol measures and neuropsychological test scores with this outlier removed are presented in Table 18. As with postdexamethasone correlations within the nonsuppressor group, the removal of this outlier eliminated most of the significant relationships between cortisol measures and test scores. Only two

TABLE 17

CORRELATIONS BETWEEN BASAL PLASMA CORTISOL MEASURES AND NEUROPSYCHOLOGICAL TEST SCORES

| Neuropsychological Test | A.M. | P.M. |
|---|---|---|
| WAIS-R Digit Span | | |
| Forward (Raw) | .04 | .01 |
| Backward (Raw) | -.02 | .10 |
| Stroop Color-Word | | |
| Word | -.11 | .02 |
| Color | -.28 * | -.25 |
| Color-Word | -.22 | -.10 |
| Interference | .02 | .21 |
| Babcock Story Recall | | |
| Immediate | -.32 * | -.23 |
| Delayed | -.15 | -.23 |
| Rey AVLT | | |
| Trial 1 | .00 | .00 |
| Trial 5 | -.25 | -.22 |
| Trial 7 (Recall) | -.16 | -.20 |
| Recognition | -.16 | -.14 |
| Benton VRT | | |
| Admin A: # Correct | -.36 * | -.30 * |
| # Errors | .16 | .14 |
| Admin D: # Correct | -.38 * | -.32 * |
| # Errors | .22 | .27 * |
| Finger Tapping | | |
| Dominant Hand | -.30 * | -.37 * |
| Nondominant Hand | -.26 * | -.35 * |
| Purdue Pegboard | | |
| Dominant Hand | -.02 | -.11 |
| Nondominant Hand | -.18 | -.12 |
| Both Hands | -.13 | -.16 |
| WAIS-R Digit Symbol | -.25 | -.14 |
| Trail Making Test | | |
| Part A (Time in Sec) | .04 | .06 |
| Part B (Time in Sec) | .14 | .07 |
| WAIS-R Block Design | -.26 * | -.15 |
| Category Test | .27 * | .25 |

*p<.05

TABLE 18

CORRELATIONS BETWEEN BASAL PLASMA CORTISOL MEASURES AND NEUROPSYCHOLOGICAL TEST SCORES WITH OUTLIER REMOVED

| Neuropsychological Test | A.M. | P.M. |
|---|---|---|
| WAIS-R Digit Span | | |
| Forward (Raw) | .03 | -.01 |
| Backward (Raw) | .05 | .22 |
| Stroop Color-Word | | |
| Word | .02 | .21 |
| Color | -.11 | -.02 |
| Color-Word | -.09 | .11 |
| Interference | -.02 | .20 |
| Babcock Story Recall | | |
| Immediate | -.17 | .00 |
| Delayed | -.01 | -.08 |
| Rey AVLT | | |
| Trial 1 | .08 | .10 |
| Trial 5 | -.13 | -.07 |
| Trial 7 (Recall) | -.04 | -.05 |
| Recognition | -.07 | -.01 |
| Benton VRT | | |
| Admin A: # Correct | -.23 | -.10 |
| # Errors | .16 | .14 |
| Admin D: # Correct | -.30 * | -.20 |
| # Errors | .22 | .27 * |
| Finger Tapping | | |
| Dominant Hand | -.07 | -.12 |
| Nondominant Hand | .02 | -.04 |
| Purdue Pegboard | | |
| Dominant Hand | -.03 | -.14 |
| Nondominant Hand | -.19 | -.12 |
| Both Hands | -.07 | -.10 |
| WAIS-R Digit Symbol | -.17 | -.01 |
| Trail Making Test | | |
| Part A (Time in Sec) | .04 | .07 |
| Part B (Time in Sec) | .11 | .02 |
| WAIS-R Block Design | -.25 | -.12 |
| Category Test | .15 | .10 |

*p<.05

statistically significant correlations remained: the correlation between a.m. cortisol and the number correct on Benton Administration D, and the correlation between p.m. cortisol and the error score on Benton Administration D. Given the number of correlations computed in this table, at least this many significant results would have been expected by chance alone.

Relationships with ACTH level

ACTH and suppressor status.

Basal ACTH measures (a.m. and p.m. on predexamethasone day) were not significantly different between suppressors and nonsuppressors ($t$=1.41, $df$=28.6, $p$=.169 for a.m.; $t$=1.74, $df$=23.7, $p$=.095 for p.m.), nor were they significantly correlated with post-dexamethasone a.m. cortisol level ($r$=.24, $p$=.065 with a.m. ACTH; $r$=.21, $p$=.118 with p.m.). Thus, they represented a measure of functioning of the hypothalamic-pituitary-adrenal system which was relatively independent of suppressor status.

Basal ACTH measures were each moderately correlated, however, with plasma cortisol values on the pre-dexamethasone day (a.m. ACTH and cortisol, $r$=.36 with outlier removed, $p$=.005; p.m. ACTH and cortisol, $r$=.30 with outlier removed, $p$=.021). Correlations were moderate as well between basal ACTH measures and pre-dexamethasone urinary free cortisol ($r$=.47, $p$=.001 with a.m. ACTH; $r$=.39, $p$=.007 with p.m. ACTH).

As expected, post-dexamethasone ACTH's differed between suppressors and nonsuppressors (for a.m. ACTH, suppressor mean=35.5 $\pm$ 17.5, nonsuppressor mean=60.3 $\pm$ 33.6, $t$=3.28, $df$=29.50, $p$=.003; for

p.m. ACTH, suppressor mean=34.9 ± 16.8, nonsuppressor mean=57.6 ± 26.0, $t$=3.66, $df$=31.56, $p$=.001).

ACTH measures in general were strikingly consistent. Basal a.m. and p.m. measures of ACTH were highly correlated with each other ($r$=.93, $p$<.001), and with corresponding post-dexamethasone ACTH levels ($r$=.87 and .88, respectively with a.m. post-dex ACTH; $r$=.83 and .87 with p.m. post-dex ACTH, all $p$<.001).

ACTH and demographic/clinical data.

Correlations between basal ACTH measures and selected demographic and clinical measures are presented in Table 19. None of the

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TABLE 19

CORRELATIONS BETWEEN BASAL ACTH MEASURES AND SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

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| Variable | A.M. | P.M. |
|---|---|---|
| Age | .17 | .16 |
| Education | .01 | .04 |
| Est. IQ | .05 | .07 |
| WAIS-R Vocab. | -.03 | -.05 |
| GAS | -.08 | -.06 |
| HDRS | -.04 | -.01 |
| Carroll | .12 | .15 |
| Beck | .08 | .04 |

None significant at p<.05

correlations with age, education, estimates of IQ, or depression severity measures were significantly different than zero.

ACTH and neuropsychological functioning.

Correlations between basal ACTH measures and neuropsychological test scores are presented in Table 20. The only significant correlations were with the Benton Visual Retention Test (Administration D) and the Purdue Pegboard (non-dominant hand). The correlation between basal p.m. ACTH and non-dominant Pegboard failed to reach significance. At the .05 level, between 2 and 3 of the 56 correlations reported here (1 in 20) would be significant by chance alone. Therefore, there appeared to be little consistent relationship between basal ACTH and neuropsychological functioning, except for a very mild relationship with the administration of the Benton that required delayed recall of visual information.

## Relationships with urinary free cortisol

Urinary free cortisol and suppressor status.

Both pre- and post-dexamethasone urinary free cortisols differed between suppressors and nonsuppressors (pre-dex means 89.4 $\pm$ 25.7 and 176.0 $\pm$ 58.6, respectively, $t$=5.92, $df$=21.26, $p$<.001; post-dex means 33.2 $\pm$ 27.0 and 95.0 $\pm$ 45.0, $t$=4.41, $df$=14.78, $p$=.001). Each urinary free cortisol measure was strongly correlated with post-dexamethasone a.m. plasma cortisol ($r$=.67, $p$<.001 with pre-dex UFC; $r$=.76, $p$<.001 with post-dex UFC; with the single plasma cortisol outlier removed correlations are .77 and .76, respectively, both $p$<.001). The two urinary free cortisol measures were also highly correlated with each

TABLE 20

CORRELATIONS BETWEEN BASAL ACTH MEASURES AND

NEUROPSYCHOLOGICAL TEST SCORES

| Neuropsychological Test | A.M. | P.M. |
|---|---|---|
| WAIS-R Digit Span | | |
| Forward (Raw) | .07 | .04 |
| Backward (Raw) | .11 | .15 |
| Stroop Color-Word | | |
| Word | -.04 | -.04 |
| Color | -.12 | -.09 |
| Color-Word | -.08 | -.03 |
| Interference | .04 | .12 |
| Babcock Story Recall | | |
| Immediate | -.23 | -.15 |
| Delayed | -.03 | -.01 |
| Rey AVLT | | |
| Trial 1 | -.11 | -.09 |
| Trial 5 | -.06 | -.09 |
| Trial 7 (Recall) | -.06 | -.05 |
| Recognition | .10 | .11 |
| Benton VRT | | |
| Admin A: # Correct | -.13 | -.12 |
| # Errors | .05 | .05 |
| Admin D: # Correct | -.31 * | -.28 * |
| # Errors | .29 * | .31 * |
| Finger Tapping | | |
| Dominant Hand | -.16 | -.13 |
| Nondominant Hand | -.12 | -.12 |
| Purdue Pegboard | | |
| Dominant Hand | -.13 | -.12 |
| Nondominant Hand | -.27 * | -.25 |
| Both Hands | -.09 | -.11 |
| WAIS-R Digit Symbol | -.13 | -.09 |
| Trail Making Test | | |
| Part A (Time in Sec) | .11 | .18 |
| Part B (Time in Sec) | .14 | .19 |
| WAIS-R Block Design | -.19 | -.16 |
| Category Test | .19 | .15 |

*p<.05

other ($r$=.87, $p$<.001).

The information obtained from urinary free cortisol measures overlapped considerably with information derived from dexamethasone suppression/nonsuppression of plasma cortisol. While the relationship between post-dexamethasone UFC and post-dexamethasone plasma cortisol was expected (the plasma measure is a subset of the 24-hour measure), the relationship to pre-dexamethasone urinary free cortisol was stronger than expected. The correlation between basal UFC and post-dexamethasone plasma cortisol is depicted in Figure 1. A pre-dexamethasone UFC above 150 mcg/24 hrs. was found in 72.2% of nonsuppressors and 0.0% of suppressors (Yate's corrected Chi-Square=24.74, $df$=1, $p$<.001). This divergence in the distribution of basal UFC's in suppressors and nonsuppressors is presented graphically in Figure 2. Given that the upper limit of normal for a 24-hour UFC is approximately 100 mcg, marked hypercortisolism appeared to be a strong predictor of dexamethasone nonsuppression.

Urinary free cortisol and demographic/clinical variables.

Correlations between UFC and selected demographic and clinical variables are presented in Table 21. Only the correlation between basal UFC and Global Assessment Scale score was significant, and at least one correlation in this matrix might be expected to be significant on the basis of chance alone. Non-linearity in the relationship between UFC and these variables, like that observed with post-dexamethasone plasma cortisol (where cortisol level above the nonsuppression threshold did not predict clinical severity), however, may have attenuated these correlations. For this reason a median split

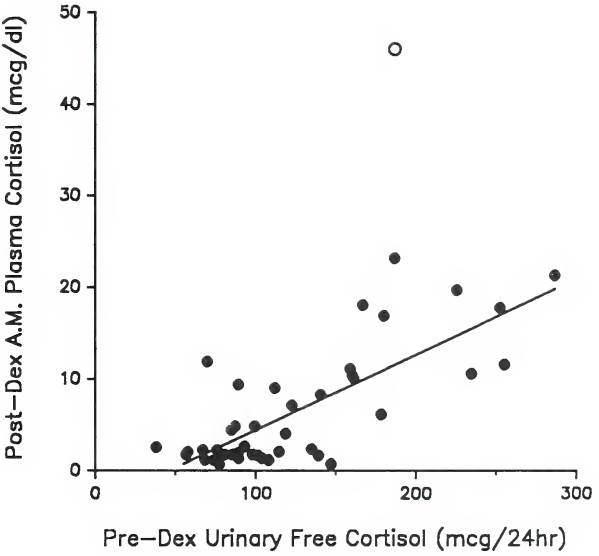


Figure 1: Correlation between Pre-Dexamethasone Urinary Free Cortisol and Post-Dexamethasone A.M. Plasma Cortisol. Correlation coefficient is .77 with the single plasma cortisol outlier removed (n=45).

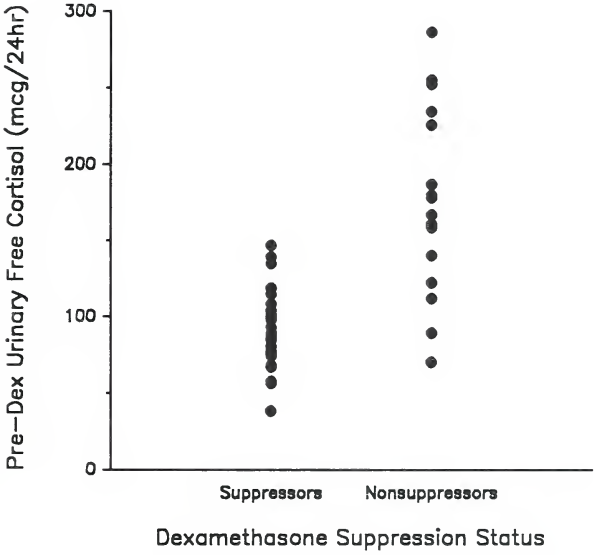


Figure 2: Pre–Dexamethasone Urinary Free Cortisol in Suppressors and Nonsuppressors.

TABLE 21

CORRELATIONS BETWEEN BASAL UFC MEASURE AND

SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

| Variable | Basal UFC | Post-Dex UFC |
|---|---|---|
| Age | .23 | .23 |
| Education | .03 | .05 |
| Est. IQ | -.01 | -.01 |
| WAIS-R Vocab. | -.05 | -.03 |
| GAS | -.36 * | -.27 |
| HDRS | .07 | .02 |
| Carroll | .25 | .18 |
| Beck | .09 | -.09 |

* $p<.05$

was performed on each of the UFC distributions, and subjects above and below the medians were compared.

For basal UFC, the distribution median of 102.4 approximated the cutoff for the upper limit of normal cortisol secretion of 100 mcg/24hrs. Thus, the median split on this data defined groups of normo- and hypersecretors. Means, standard deviations, and probability values for t-test comparisons between these two groups are presented in Table 22. Dichotomous demographic and clinical variables which were not included in correlational analyses are included in this table.

TABLE 22

COMPARISON OF PATIENTS ABOVE AND BELOW MEDIAN OF BASAL UFC DISTRIBUTION ON SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

(N = 46)

| Variable | Below Median | Above Median | p |
|---|---|---|---|
| Age | 43.9 ± 17.9 | 57.1 ± 16.2 | .012 |
| Sex (% female) | 87.0% | 60.9% | NS |
| Education | 13.5 ± 3.4 | 13.4 ± 3.2 | NS |
| Est. IQ | 107.6 ± 12.7 | 109.4 ± 13.6 | NS |
| WAIS-R Vocab. | 12.0 ± 3.0 | 12.4 ± 3.2 | NS |
| GAS | 50.0 ± 7.7 | 42.3 ± 7.3 | .001 |
| HDRS | 28.0 ± 5.6 | 31.2 ± 5.9 | NS |
| Carroll | 33.3 ± 10.8 | 37.5 ± 12.4 | NS |
| Beck | 29.5 ± 13.4 | 34.8 ± 11.3 | NS |
| Bipolar Disorder | 13.0% | 13.0% | NS |
| Melancholia | 52.2% | 47.8% | NS |
| Psychoticism | 0.0% | 26.1% | .003 |
| Axis II Disorder | 69.6% | 34.8% | .039 |
| Nonsuppressors | 8.7% | 69.6% | <.001 |

Significant differences between UFC normo- and hypersecretors were observed in age, Global Assessment Scale score, and the likelihood of psychoticism, Axis II (personality) disorder, and nonsuppression. Like

nonsuppressors, hypersecretors were older, appeared more dysfunctional, and were more likely to be diagnosed psychotic. Hypersecretors were less likely to be diagnosed as having a personality disorder, a non-significant tendency observed in comparisons between suppressors and nonsuppressors. Differences in endogenicity (Carroll) and subjective depression (Beck) which were observed between suppressors and nonsuppressors, however, were not observed between normosecretors and hypersecretors.

Comparisons of those patients above and below the median of the post-dexamethasone UFC distribution are presented in Table 23.

No clinical or demographic differences were observed between those above and below the median of post-dexamethasone UFC, except in the percentage of nonsuppressors.

Although the post-dexamethasone UFC is highly correlated with post-dexamethasone a.m. plasma cortisol ($r$=.76, vide supra), the same differences observed between suppressors and nonsuppressors were not found in the comparison of those above and below the median post-dexamethasone UFC.

Urinary free cortisol and neuropsychological functioning.

Correlations between UFC and neuropsychological test scores are presented in Table 24. Significant correlations were observed between basal UFC and scores on the Rey trials 5 and 7, all subscores from the Benton, Finger Tapping, Purdue Pegboard (non-dominant and both hands only), WAIS-R Digit Symbol, Trails B, WAIS-R Block Design, and the Category Test. Correlations greater than .40, however, were observed with only Rey Trial 5, Benton Administration D, and the Category Test.

TABLE 23

COMPARISON OF PATIENTS ABOVE AND BELOW MEDIAN OF POST-DEXAMETHASONE UFC DISTRIBUTION ON SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

(N = 38)

| Variable | Below Median | Above Median | p |
|---|---|---|---|
| Age | 46.3 ± 17.9 | 53.3 ± 16.2 | NS |
| Sex (% female) | 78.9% | 63.2% | NS |
| Education | 13.2 ± 3.9 | 13.7 ± 2.7 | NS |
| Est. IQ | 108.5 ± 15.2 | 110.3 ± 14.0 | NS |
| WAIS-R Vocab. | 12.1 ± 3.4 | 12.1 ± 3.2 | NS |
| GAS | 48.3 ± 6.7 | 44.6 ± 7.5 | NS |
| HDRS | 28.8 ± 5.4 | 30.0 ± 7.0 | NS |
| Carroll | 34.1 ± 12.2 | 35.8 ± 12.3 | NS |
| Beck | 29.5 ± 9.6 | 34.2 ± 14.3 | NS |
| Bipolar Disorder | 21.1% | 15.8% | NS |
| Melancholia | 52.6% | 47.4% | NS |
| Psychoticism | 5.3% | 21.1% | NS |
| Axis II Disorder | 42.1% | 42.1% | NS |
| Nonsuppressors | 5.3% | 57.9% | .002 |

Post-dexamethasone UFC was significantly correlated with only the Rey (Trials 1 & 5), the Benton (A error & D, both scores), and Finger Tapping. Only correlations with Rey trial 5 and Benton administration D were greater than .40. Both basal and, to a lesser extent, post-

TABLE 24

CORRELATIONS BETWEEN UFC MEASURES AND

NEUROPSYCHOLOGICAL TEST SCORES

| Neuropsychological Test | Basal UFC | Post-Dex UFC |
|---|---|---|
| WAIS-R Digit Span | | |
| Forward (Raw) | .11 | .13 |
| Backward (Raw) | -.05 | -.04 |
| Stroop Color-Word | | |
| Word | -.20 | -.15 |
| Color | -.22 | -.12 |
| Color-Word | -.27 | -.14 |
| Interference | -.13 | .00 |
| Babcock Story Recall | | |
| Immediate | -.02 | -.15 |
| Delayed | -.09 | -.16 |
| Rey AVLT | | |
| Trial 1 | -.24 | -.35 * |
| Trial 5 | -.49 * | -.47 * |
| Trial 7 (Recall) | -.30 * | -.24 |
| Recognition | -.25 | -.05 |
| Benton VRT | | |
| Admin A: # Correct | -.37 * | -.27 |
| # Errors | .37 * | .32 * |
| Admin D: # Correct | -.45 * | -.43 * |
| # Errors | .36 * | .40 * |
| Finger Tapping | | |
| Dominant Hand | -.33 * | -.34 * |
| Nondominant Hand | -.34 * | -.34 * |
| Purdue Pegboard | | |
| Dominant Hand | -.22 | -.23 |
| Nondominant Hand | -.35 * | -.29 |
| Both Hands | -.29 * | -.17 |
| WAIS-R Digit Symbol | -.29 * | -.23 |
| Trail Making Test | | |
| Part A (Time in Sec) | .15 | .09 |
| Part B (Time in Sec) | .36 * | .30 |
| WAIS-R Block Design | -.37 * | -.31 |
| Category Test | .43 * | .15 |

*p<.05

dexamethasone UFC, were related to the same subset of tests which were found to differ most robustly between suppressors and nonsuppressors.

A multivariate comparison of basal UFC normsecretors and hypersecretors was undertaken next. Because these groups differed in age, age was employed as a covariate. Results of this analysis again demonstrated the significant multivariate relationship between age and neuropsychological test score (Wilk's Lambda=.424, df=12,32, p=.002). The effect of normo- vs. hypersecretion, however, was not significant (Wilk's Lambda=.661, df=12,32, p=.232).

Multivariate comparison of neuropsychological performance based on the median split of post-dexamethasone UFC also revealed a significant effect for the covariate, age (Wilk's Lambda=.266, df=12,24, p<.001), but a non-significant effect for high vs. low post-dexamethasone UFC (Wilk's Lambda=.719, df=12,24, p=.665).

In general, basal urinary free cortisol efficiently predicted plasma cortisol response to dexamethasone. Clinical and neuropsychological distinctions, however, appeared more closely related to the suppressor/nonsuppressor dichotomy, than to the normosecretor/ hypersecretor dichotomy.

Patients excluded from basal urinary free cortisol analyses.

Fourteen of 60 (23.3%) of patients did not complete the pre-dexamethasone urine collection necessary to assess basal UFC. Twenty-two of 60 (37.6%) did not complete the post-dexamethasone collection.

Because the pre-dexamethasone UFC was a critical measure in this study (from the standpoint of providing information about patients' typical cortisol levels), a supplemental analysis of the

characteristics of those who did and did not complete this initial urine collection was undertaken.

The percentage of nonsuppressors among those who did not complete the pre-dexamethasone urine collection was virtually identical to that among those who completed the collection (35.7% vs. 39.1%, respectively, Yates' Corrected Chi-Square=0.00, df=1, p=1.00). Those with incomplete collections, however, had lower Hamilton scores (t=2.47, df=58, p=.016), higher GAS scores (t=2.10, df=57, p=.040), and were more likely to be diagnosed with a bipolar disorder (42.9% vs. 13.0% in the completer group, Yates' Corrected Chi-Square=4.24, df=1, p=.039). On neuropsychological tests, these excluded patients had lower WAIS-R Digit Span scores (forward & backward, t=3.10, df=58, p=.003 and t=2.90, df=58, p=.005, respectively) and lower Stroop Interference scores (t=1.96, df=57, p=.055). Although the Paced Serial Addition Test was not included in the overall data analysis, examination of these scores here revealed that excluded patients tended to have lower scores on the first trial of this test (t=1.86, df=47, p=.069) and that they had significantly lower scores on the second trial (t=2.17, df=47, p=.035).

Excluded subjects, then, were less depressed, more globally functional, and more likely to be bipolar. Despite appearing less depressed, they had consistently lower scores on tests of attention and concentration. No differences were found in any other areas of cognitive functioning. Paradoxically, basal UFC analyses were biased in favor of inclusion of the most severely depressed patients. The effects of attention/concentration on neuropsychological performance

among those with valid basal UFC's was most likely attenuated by the exclusion of some lower scorers.

# CHAPTER 4

# DISCUSSION

## Summary of findings

The results of this study reveal that particular biological subtypes of depressed patients show specific deviations in cognitive functioning that may have important psychobiological implications. In particular, DST nonsuppressors are significantly more likely than suppressors to perform poorly on tasks involving nonverbal memory, learning, manual dexterity, mental sequencing, abstract concept formation, and visuospatial conceptualization. Moreover, nonsuppressors report more subjective distress, have longer hospitalizations, and are more likely to receive ECT than suppressors. These findings are independent of morning and evening levels of ACTH and pre-dexamethasone cortisol. Similar types of cognitive dysfunction are correlated with 24-hour excretion of urinary free cortisol; however, the information obtained from UFC overlaps considerably with that obtained from dexamethasone suppression/nonsuppression of cortisol. In general, cognitive deficits appear to be more strongly related to the latter index. HPA abnormalities and cognitive impairment appear to be products of both depression and age, although each of these factors contributes independently. In the discussion which follows, I will elaborate upon these general conclusions, and speculate about the mechanisms involved in producing these neuropsychological disabilities, and the role of age in HPA and cognitive disturbances. To accomplish this, the study results will be presented in a manner similar to the hypotheses and results sections:

(1) DST findings; (2) ACTH findings; (3) UFC findings.

Cognitive profile of entire sample

Examination of the profile of neuropsychological functioning in the entire sample reveals that very few of the patients were impaired on any of the WAIS-R subtests, and that performance on individual subtests was consistent with estimated IQ based on the Ammons Quick Test. In order to determine whether performance in this sample was truly representative of performance in the population of depressed inpatients in general, these data were compared to previous studies. WAIS-R scores in depressed samples have been reported to be both lower than those of normal controls and similar to schizophrenic samples (Payne, 1973; Miller, 1975), and no different from normal controls (Granick, 1963). Other studies have compared IQ scores in the same patient during periods of illness and remission, and noted higher IQ scores associated with euthymia (Miller, Small, & Milstein, 1981). Although this has been interpreted as indicating a state-related decrement in intelligence (Miller, 1975), recent studies suggest that higher scores on the second administration may represent practice effects (Donnelly, Murphy, Goodwin & Waldman, 1982). Data from broad-based neuropsychological batteries, however, provide substantial and consistent evidence for cognitive decline during the depressive episode. For example, Silverstein and Meltzer (1983) reported that schizophrenic and depressed patients were equivalently impaired on the Luria-Nebraska and Halstead-Reitan neuropsychological batteries. Abrams and Taylor (1984), using the same neuropsychological battery,

found that compared to controls, melancholic patients were significantly more impaired in all areas tested. The more clearcut findings observed with neuropsychological measures than with intelligence testing, may be because neuropsychological batteries tap a broader range of psychomotor and cognitive functions than those typically encompassed by IQ tests.

Dexamethasone suppression test

Cognitive measures.

One of the major findings of this study is the relationship between disturbances in feedback inhibition and cognitive dysfunction. DST nonsuppressors were not only impaired on more of the neuropsychological measures than suppressors (10 vs. 6), but performed consistently worse on specific measures of learning (Rey AVLT), visual-spatial memory (Benton), fine motor coordination (Purdue Pegboard), sequential reasoning (Trail Making B), logical reasoning/concept formation (Category Test), and visual-spatial organization and reasoning (Block Design). Consistent differences were not observed on other measures of neuropsych functioning: simple motor speed (Finger Tapping), psychomotor speed (Digit Symbol), simple sequencing (Trail Making A), attention (Digit Span) or attentional interference (Stroop), or narrative memory (Babcock). These findings indicate that the poorer performance of nonsuppressors is not due solely to psychomotor retardation, or disturbances in attention or concentration. Rather, this profile of cognitive dysfunction suggests disruption of higher order cognitive processes.

Despite the long-standing evidence of cognitive impairment during the acute expression of affective illness in general, few studies have explored the relationship between cognitive functioning and biological markers of depression. The present study is the first to systematically document a relationship between DST nonsuppression and cognitive dysfunction in depressed patients. Although prior studies (Brown & Qualls, 1981; Reus, 1982; Winokur, Black, & Nasrallah, 1987) have reported that depressed patients with feedback disturbances are more impaired than those with intact feedback, methods of assessing cognitive function were based on clinical impressions or ratings of attention and concentration, and relevant clinical and demographic variables were not controlled for. Related observations lend support to the notion that depressed patients with HPA disturbances or symptom patterns reflective of HPA disturbance (e.g., melancholia, endogenicity) may have specific deficits in cognitive function. For example, Rubinow et al (1984; discussed below) have related poorer performance on the Halstead Category Test to HPA hyperactivity, as measured by 24-hour urinary free cortisol. Other studies have not focussed specifically on suppressor/nonsuppressor differences, but do provide evidence of cognitive impairment in a subgroup of patients in which symptomatology has been shown to covary with pituitary-adrenal activity. Cornell and colleagues (1984) demonstrated disturbances in psychomotor performance in both melancholic and nonmelancholic patients, relative to controls, with melancholic patients manifesting an additional cognitive impairment not evident in the other two groups. Endogenous patients have also been reported to perform more poorly than

matched nonenodgenous patients on a standard neuropsychological battery (Rush, Weissenburger, Vinson, & Giles, 1983).

In contrast, other studies have reported no relationship between suppression status (Caine, Yerevanian, & Bamford, 1984), or poorer performance in DST suppressors (Beckwith, 1977; Silberman, Weingartner, Targum, & Byrnes, 1985). Differences in patient samples and methodology may account for these inconsistencies. For example, in these latter studies, patient samples were relatively young (mean age < 40), not very diagnostically homogeneous (i.e., included patients with dysthymic disoder, schizoaffective disorder, and adjustment reaction), and only mildly to moderately depressed (based on objective and subjective measures). Furthermore, although matched for age and education, suppressors and nonsuppressors were not equated for IQ in any of these studies. Additionally, determination of suppressor status was based on blood samples obtained at 4 p.m. and 11 p.m. Previous studies by the NIMH CRB Psychobiology Depression Program-Biological Studies group have shown that sampling at these later points on the post-dexamethasone day may substantially reduce the specificity of the DST; in fact, in the CDS, 35% of normal controls were classified as nonsuppressors based on these later samples (vs. about 12% for a.m. samples only [Stokes et al., 1984]). Finally, the neuropsychological batteries employed in most of these studies either measured only a few functions or were heavily loaded with tests reflecting verbal and left-hemisphere tasks, functions generally resistant to all but the most severe organic disorders. Because these prior neuropsychological studies have used such diverse methodologies in a small number of

subjects and because age may be a confounding factor, these findings should be considered tentative. What is clear from these studies is that measuring a variety of cognitive processes in homogeneous samples of depressed patients is necessary in order to detect differential cognitive impairment in HPA sutypes.

Types of deficits.

It was originally hypothesized that nonsuppressors would show a relative preponderance of visual-spatial, visual-ideational deficits, similar to data obtained on patients with Cushing's syndrome (CS). Poorer performance on Block Design, the Benton Visual Retention Test, and Trails B are consistent with this hypothesis. However, closer examination of the functions that are disturbed indicates that a simple model of right hemispheric dysfunction does not adequately characterize the pattern of deficits observed in nonsuppressors in this study. This pattern is more accurately described by the locus of dysfunction within hemispheres. In this case, nonsuppressors manifest patterns of dysfunction reflective of greater anterior relative to posterior cortical dysfunction, with evidence of specific frontotemporal disturbances. This constellation has been reported in other studies of severely depressed patients (Flor-Henry, 1983; Silverstein & Meltzer, 1983), and deficits in attention, concept formation/reasoning, fine motor control, and non-verbal short-term memory, as well as learning, are consistent with disturbances of these loci. The neuropsychological profile of adult DST nonsuppressors in the present study is consistent with recent data obtained with depressed children at the University of Michigan (N. Alessi, personal communication, April, 1988).

Comparison to Cushing's syndrome patients.

The findings in the present study are, at first glance, similar to the deficits reported in patients with CS (Starkman & Schteingart, 1981; Starkman, Schteingart, & Schork, 1986; Whelan, Schteingart, Starkman, & Smith, 1980); however, lower order functions were spared in the depressed patients, whereas both higher and lower functions were compromised in the CS patients. Closer examination of the CS data (Whelan, Schteingart, Starkman, & Smith, 1980) reveals that although selected measures were markedly abnormal, declines were obvious in all tests of higher and lower functions, including gross impairment in the WAIS-R Vocabulary subtest (28% of the patients were impaired). Because the Vocabulary subtest is generally very robust under conditions of all but the most severe brain injury (Gonen & Brown, 1968), these findings suggest that metabolic complications in some of the patients may have produced gross and diffuse organic dysfunction, and that neuropsychological performance in these patients may reflect organicity per se, rather than the effects of hypercortisolism.

The pattern of deficits noted in the CS patients are consistent with the relative preservation of cognitive functions in other conditions of diffuse encephalopathy (e.g., closed head injury, Alzheimer's disease, etc.), in which language and verbal skills are more resistant to the insult than nonverbal reasoning or visual-constructional functions (Walsh, 1978). Moreover, a similar profile of greater declines in nonverbal than verbal cognitive functions is seen in normal adults with advancing age (Wechsler, 1958).

Differences in the pathophysiology and speculated pathogenesis of

the hypercortisolism seen in CS patients vs. depressed patients may also contribute to differential cognitive performance in these two groups. Most of the patients in the Whelan et al. study (1980) had CS due to pituitary hyperfunction. In patients with adrenal hyperfunction secondary to increased ACTH secretion by the pituitary (Cushing's disease), plasma concentrations of both ACTH and cortisol are consistently elevated, and the setpoint for feedback mechanisms is markedly increased (i.e., very high levels of corticosteroid are required to minimally suppress ACTH release). Although the pathophysiology of HPA dysregulation in depression has not been definitively established, studies conducted at different levels of the system, suggest that the primary source for the dysregulation is at or above (most likely, the hippocampus) the level of the hypothalamus, and drives the hypothalamus to hypersecrete CRH. Evidence compatible with this notion is derived from the data of Nemeroff et al. (1984) which showed that immunoreactive CRH is elevated in the CSF of some depressed patients. Additionally, studies by Gold and coworkers at the NIMH (Gold et al., 1984, 1986) have shown that despite the hypothalamic overdrive, levels of ACTH remain normal. This "normal" plasma ACTH level in depression suggests either down-regulation of the corticotropes over the course of the illness, or normal corticotropes caught in the balance between negative feedback exerted by hyperplastic adrenals from below and a predominating excess of CRH from above. The net result of this stimulation is chronic and repeated hyperstimulation of the adrenal cortices, and over time, a functionally hyperactive and probably anatomically hypertrophied adrenal cortex. Thus, in CS of

pituitary etiology, levels of CRH are normal, but ACTH and cortisol secretion are excessive. In depression, CRH levels appear to be elevated, ACTH levels may be normal (or at least normalize over time), and cortisol is hypersecreted.

Differences in the degree and duration of cortisol hypersecretion may also account for differential cognitive performance in CS vs. depressed patients. Although many of the plasma cortisol levels in the present study were clearly in the CS range (>30 mcg/dl) in the morning, a diurnal variation in secretory activity (lower levels in the afternoon) was generally present. The diurnal variation in cortisol secretion is generally absent in patients with CS (i.e., hypersecretion is relatively constant). This difference is reflected in an upper limit for UFC excretion of 286.5 mcgg/24 hr in the present study vs. levels of over 1000 mcg/24 hr for CS patients in the Starkman series. Moreover, the hypercortisolism in depression has generally been present for one to two months at the time the patient presents to the clinic. The insidious onset of CS usually obscures the duration of disease processes; however, initial signs and symptoms have generally been present for at least two years before the patient is treated (Bondy, 1985). Finally, the DST abnormality found in depressive illness is more subtle than that found in Cushing's disease. In depressed patients, the HPA system shows temporary suppression and early escape from this suppression. Furthermore, the HPA system is responsive to stress (e.g. hypoglycemia challenge), while it is refractory to such challenges in Cushing's disease.

Clinical measures.

Another interesting difference between DST nonsuppressors and suppressors is the greater degree of self-reported depression (e.g., Beck Depression Inventory, Raskin Mood Scale) by the former group, despite no evidence of this trend with objective measures (Hamilton Depression Scale). Attempts in the literature to relate clinical severity of depression to feedback disturbances of the HPA system or hypersecretion of cortisol have produced inconsistent results. Although Carroll and colleagues (1968) initially found a correlation between resistance to suppression and clinical severity, he (Carroll, 1976; Carroll & Davies, 1970) and others (Giles & Rush, 1982; Targum, Byrnes, & Sullivan, 1983) subsequently have not been able to clearly and consistently differentiate suppressors and nonsuppressors based on Hamilton Depression Scale scores. In studies where differences in severity have been observed (Davis et al., 1981; Feinberg & Carroll, 1984; Reus, 1982), the usual difference between HDS score in suppressors and nonsuppressors was slight (usually less than 3) and generally not statistically significant. However, other recent studies have shown a gradual increase in rates of nonsuppression and absolute postdexamethasone cortisol levels across different subtypes of depression, i.e., from those with uncomplicated grief or dysthymic disorder to those with major depresssion without melancholia, major depression with melancholia, major depression with psychotic features, and severely suicidal depressives (Arana, Baldessarini, & Ornstein, 1985; Evans, Burnett and Nemeroff, 1983). Thus, post-dexamethasone cortisol levels may actually reflect a qualitative or diagnostic classification difference rather than a quantitative difference in

severity. In general then, previous studies indicate that severe depression is neither necessary nor sufficient for DST nonsuppression to occur. Thus, patients in the low to moderate range for severity may have HPA disturbances; for example, in the present study, Patients #27 and #60 had Hamilton scores of 22, and were both clearly nonsuppressors. On the contrary, severely depressed patients can have normal HPA function; for example, Patients #14 and #29 had Hamilton scores of 46 and 40, respectively, and both showed a normal cortisol response to dexamethasone.

Although differences betweeen suppressors and nonsuppressors on both the Beck and Raskin scales in the present study may reflect the weaknesses inherent in self-report measures, studies in normal populations, and other studies of depressed patients, do suggest an association between cortisol and mood. For example, Lundberg and Frankenhaeuser (1980) observed in a group of college students that HPA activation (reflected in elevated UFC) was associated with self-reported negative feelings of distress (boredom, impatience, fatigue, irritability, lack of interest, and diminished concentration), whereas sympathoadrenalmedullary activation was associated with feelings of alertness and activation. Similarly, Ballenger and colleagues (1980) reported a significant positive correlation ($\underline{r}$=.44, $\underline{p}$<.05) between mean 24-hour UFC excretion and trait depression in a group of normal subjects. While these data must be considered preliminary, such findings in a "normal" population do lend additional support to the potential role of the HPA system in pathological affective regulation. Rubinow et al. (1984) observed significant correlations between

severity of daily depression and 8 a.m. plasma cortisol values in 10 of 17 patients with affective illness. This finding is particularly interesting given the episodic nature and variability of cortisol at this time of the day, and supports the notion that alterations in HPA activity may accompany changes in severity in some patients, while corresponding only to the presence or absence of depression in others.

Taken together, these findings suggest that suppression and nonsuppression may represent qualitatively different manifestations of depression, rather than endpoints on the continuum of severity. In other words, the experience or expression of components of the depressive syndrome may covary with measures of HPA activity, and may or may not covary with the severity of the episode.

In addition, the findings of a greater likelihood of receiving ECT as a primary treatment modality and the longer median hospital stay for nonsuppressors vs. suppressors, also indicate that dimensions of depressive illness other than symptom number and intensity may be associated with HPA dysregulation. These findings are consistent with other reports of longer hospitalizations in DST nonsuppressors (Brown, 1987), and the finding of a lower rate of recovery following placebo in outpatient nonsuppressors (Shrivastava, Schwimmer, Brown, & Arato, 1985). Suppressors and nonsuppressors did not, however, differ in family history (i.e., Winokur's classification) of affective illness, as originally hypothesized. This latter finding is in contrast to a report by Schlesser et al. (1980), but consistent with subsequent reports by Asnis et al. (1982), and Zimmerman et al. (1986), and suggests that DST nonsuppressors do not necessarily have a higher

morbid risk for depression.

Basal plasma cortisol.

Although pre- and post-dexamethasone cortisol levels were moderately correlated, and nonsuppressors had significantly higher basal plasma cortisol levels than suppressors, cognitive performance was not related to basal plasma cortisol. These findings indicate that although output from various levels of the HPA regulatory system may be associated in some patients, not all are equally relevant to behavior. Basal cortisol is a global manifestation of the HPA system activity, which is influenced by multiple outputs at all levels of the system, from the hypothalamus to the adrenal cortex. Moreover, the variability of cortisol at this time of day (9 a.m.) may obscure any existing relationship, although single-stick measures were representative of 24-hour UFC output. The dexamethasone suppression test provides a means of assessing a specific aspect of this system; i.e., disturbed feedback mechanisms involving glucocorticoid receptors predominantly in the pituitary, and perhaps, altered regulation of the HPA axis at the level of limbic-hypothalamic connections. Although several investigators have reported a dissociation between single-sample basal measures of cortisol production and post-dexamethasone cortisol levels (Brown, Keitner, Qualls, & Haier, 1985; Kathol, Winokur, Sherman, Lewis, & Schlesser, 1984), others have found that single-sample basal plasma cortisol levels were elevated in depressed nonsuppressors vs. suppressors (Asnis, Sachar, Halbreich, Nathan, & Halpern, 1981; Carroll, Curtis, & Mendels, 1976; Stokes, Pick, Stoll, & Nunn, 1975). Whether the dissociation between these two measures actually reflects

two different, but not necessarily orthogonal HPA abnormalities, or whether the relationship between basal cortisol and feedback disinhibition changes over the course of a depressive episode is unclear. It may be that during the early stages of a depression, basal activity of the system establishes a range within which post-dex cortisol levels are free to fluctuate. Over time, however, chronically elevated basal cortisol may alter dexamethasone pharmacokinetics by inducing hepatic enzymes which enhance metabolism of the exogenous steroid and decrease the suppressing effect of exogenous corticosteroid.

Post-dexamethasone cortisol levels.

Contrary to the original hypothesis, no relationship was observed between post-dexamethasone cortisol levels and cognitive performance in nonsuppressing patients, when post-dex cortisol was treated as a continuous variable. Nor was post-dex cortisol related to severity of depression or age in the nonsuppressor group. These data indicate that severity of endocrine dysregulation (and concomitant cognitive disturbances) are not related to absolute degree of cortisol suppression by dexamethasone, and provide justification for the clinical practice of treating suppressor status as a dichotomous categorization. Perhaps, as suggested by Carroll and colleagues (1976), the dimension of time in the suppression response may be more important in assessing the degree of HPA abnormality, i.e., with increasing severity of illness, the escape from dexamethasone suppression occurs earlier in the day. If this graded series of responses in a sample does actually reflect increasing severity of

depression or neuroendocrine perturbation, then it makes little sense to assume that a patient with a post-dex value of 12 mcg/dl at a particular time is twice as abnormal as a patient with a level of 6mcg/dl at the same point in time.

Basal ACTH findings

No relationship was observed between basal plasma ACTH measures and cognitive performance. This finding is not surprising in light of the fact that most patients had basal ACTH levels within the normal range of 10 to 100 pg/ml; only 8 of 60 (13.3%) had basal a.m. levels above the normative cut-off. Despite findings of enhanced arousal and attention in animals given pharmacologic doses of non-steroidogenic fragments of ACTH, and despite findings to the contrary in patients with Cushings disease (chronically high physiologic levels of ACTH), there is no data in the literature to suggest that variations within the normal range are correlated with cognitive performance.

While it may be optimistic to expect that single-sample values of ACTH are representative of 24 hour ACTH production, 24-hour cannula studies would have been too costly, too time consuming and too invasive for inclusion in the present study. Since ACTH is secreted episodically and has a short half-life, it is possible that sampling times in the present study may have missed the ACTH peak. However, it is highly unlikely that this ACTH peak was missed in the majority of patients studied. Most importantly, though, all four ACTH samples (pre-dexamethasone a.m. and p.m.; post-dexamethasone a.m. and p.m.), were highly intercorrelated, and demonstrated both diurnal rhythm and

the expected effect of dexamethasone, suggesting that they were indeed representative of general pituitary activity. In addition, the finding that ACTH levels, in general, are not elevated in depressed patients has been similarly noted in previous studies (Charlton, Leake, Wright, Griffiths, & Ferrier, 1987; Fang, Tricou, Robertson, & Meltzer, 1981; Linkowski et al., 1985) and is consistent with the notion that compensatory changes in the HPA axis over time cause normalization of ACTH (Gold et al., 1986). Based on this model of sequential changes in the HPA system, we might expect that patients with a short history of depression would have higher ACTH concentrations than those with a long history. This data was not, however, available for testing in the present study.

Basal a.m. ACTH concentrations did not correlate closely with corresponding cortisol ($\underline{r}$=.32), and there was only a partial overlap between the group with elevated cortisol and the group with elevated ACTH. This finding of a dissociation between ACTH and cortisol is consistent with previous reports; for example, following hemorrhage in dogs (Gann, 1979), with increased intracranial pressure (Feibel, Kelly, Lee, & Woolf, 1983) and during the morning peak in humans (Fehm, Klein, Holl, & Voigt, 1984), and in depressed patients (Fang, Tricou, Robertson, & Meltzer, 1981; Kalin, Weiler, & Sheldon, 1982; Linkowski et al., 1985; Yerevanian & Woolf, 1983). These findings suggest that the hypercortisolism associated with depression may either be centrally-determined, or mediated by some other pituitary factor, perhaps another POMC fragment.

UFC findings

The major finding with regard to 24 hour urinary free cortisol is that basal UFC is highly correlated with post-dexamethasone plasma cortisol. Thus, UFC predicts, with a high degree of accuracy, the results of the dexamethasone suppression test. The relationship between UFC and clinical characteristics and neuropsychological functioning is not as clear cut, or as strong, as the relationship between dexamethasone suppression/nonsuppression and these variables. Where relationships exist, they are very similar. Hypersecretors of UFC are older, more functionally impaired, more likely to be diagnosed as psychotic, and less likely to carry a concomitant personality disorder diagnosis. Basal UFC is correlated with many of the same tests which were found to differentiate suppressors and nonsuppressors. When age is adjusted for, however, systematic differences between UFC hypersecretors and normosecretors are eliminated. This latter finding indicates that the relationship between UFC and these cognitive variables is strongly mediated by differences in age. Rubinow and colleagues (1984) reported similarly that age accounted for a greater percentage of the variance of Category Test errors than hypercortisolism in 29 depressed patients. They concluded that UFC hypersecretion and cognitive impairment are both "products of the interaction between age and diagnosis" because the effect of age on Category Test performance was significantly different in patients vs. normal controls. The lack of an effect of age on performance in the control group may reflect a selection bias because significant age effects have been reported by others (Lewinsohn, 1973 [cited in Lezak,

1983]; Pauker, 1977). However, the finding of an interaction between age and UFC excretion in depressed patients is consistent with recent studies (Anton, 1987; Carroll, Curtis, Davies, Mendels, and Sugerman, 1976; Stokes et al., 1984). This relationship has not been observed in elderly healthy persons under normal conditions (Blichert-Toft, 1978), however, elderly persons under stress have been reported to excrete larger amounts of UFC than similarly stressed middle-aged persons (Jacobs, Mason, Kosten, Brown, & Ostfield, 1984). Two mechanisms have been suggested to account for the relationship between aging and UFC hypersecretion in depressed or stress individuals. Asnis and coworkers (1981) attribute this finding to an age-related decline in brain concentrations of norepinephrine (NE) (a neurotransmitter that is considered to be tonically inhibitory in the regulation of ACTH) interacting with an NE deficiency related to depression. A more relevant mechanism, however, may involve a stress-activated change in HPA function in conjunction with an age-related reduction of glucocorticoid receptors at the level of the hippocampus (Sapolsky, Krey, & McEwen, 1983).

Finally, because a number of patients (14 of 60) appeared to be noncompliant with the 24-hour urine collection for UFC (based on creatinine data), I wondered whether this group manifested any unique demographic or clinical characteristics (e.g., older, more depressed, psychotic, or functionally impaired) compared to patients with complete collections. In fact, this group was less severely depressed (lower Hamilton scores and Beck scores) and less functionally impaired (higher GAS ratings) than the group of compliant patients. Moreover, these

patients showed poorer performance on the Digit Span (both forward and backward), the Stroop (interference score), and Paced Auditory Serial Addition (Parts A and B), suggesting that they had disturbances in attention and concentration (but no disruption of higher order processes), which carried over to the urine collection procedure. These patients were also more likely to be diagnosed as bipolar (mixed or depressed).

Relationship between HPA dysregulation and cognitive performance.

The relationship between cognitive performance and HPA dysregulation may be either causal or indirect. With regard to the former, increased levels of free cortisol may produce cognitive impairment by acting directly on brain tissue. My original hypothesis that hypercortisolism might be directly involved in the regulation of cognitive processes was based on several considerations. First, cognitive impairment has been reported in patients with Cushing's syndrome (Whelan, Schteingart, Starkman, & Smith, 1980), with more severe deficits associated with higher cortisol/ACTH hormone ratios (Starkman & Schteingart, 1981). Second, exogenous administration of corticosteroids to rodents produces disruption in learning and retention in various experimental paradigms. Third, administration of corticosteroids has been found to alter spontaneous neural activity as manifest by decreased hippocampal electrical activity (Pfaff, Silva, & Weiss, 1971), and increased latency of synaptic neurotransmission (Reichlin, 1974). Fourth, elevated endogenous levels of cortisol have been associated with disruptions of sensory processes (Henkin, 1975).

Finally, hypersecretion of UFC in depressed patients has been associated with impaired performance on a concept formation task (Rubinow, Post, Savard, & Gold, 1984).

However, in the present study, cognitive disturbances do not appear to be the byproducts of hypercortisolism per se. Rather, deficits in higher order cognitive processing are more strongly associated with dexamethasone resistance and with advanced age. This latter finding suggests that both HPA activation and cognitive impairment may be downstream effects of a CNS disturbance. Most current research points to the hippocampus as the likely locus of these perturbations, because this limbic structure is both a major regulatory site for HPA activity and for learning and memory processes. The nature of the link between neuropsychological dysfunction and dexamethasone resistance is discussed below.

Model linking cognitive disturbances and HPA dysregulation.

The most intriguing explanation for both cognitive disturbances and HPA dysregulation in some depressed patients is based on work performed by McEwen, Sapolsky, Landfield, and others. The basic premise for this model is that in certain individuals (e.g., older persons), a major predisposing stressor prior to the onset of depression, or the psychological distress associated with depression per se, produces excess secretion of cortisol, and increased brain (in particular, hippocampal) exposure to glucocorticoids. Cumulative exposure to elevated circulating levels of cortisol has been shown to produce not only degenerative loss of neurons in the senescent

hippocampus (Landfield, Braun, Pitler, Lindsay, & Lynch, 1981; Landfield, Rose, Sandles, Wohlstadter, & Lynch, 1977; Landfield, Waymire, & Lynch, 1978), but also an auto-regulatory decrease in the number of glucocorticoid receptors in the hippocampus (Sapolsky, Krey, & McEwen, 1984). These degenerative changes in hippocampal neurons and receptors further compound the involutional changes that occur with advancing age. For example, Ball (1977) has measured neuronal loss in the hippocampus and reported a linear decrease of over 25 percent between 49 and 95 years of age. These morphologic changes are associated with a slow decline in tests measuring reaction time, learning, memory, and speed of processing information. In addition to cell loss per se, the concentration of glucocorticoid receptors in the hippocampus diminishes with normal aging; however, this receptor loss is generally below the threshold for impairing HPA feedback inhibition. But, when aging and depression interact, the incidence of HPA dysregulation and cognitive impairment increase dramatically. Thus, in senescent individuals with hippocampal cell and glucocorticoid receptor numbers already close to the threshold for cognitive decline and feedback resistance, smaller amounts of stress or (distress) may be needed to produce these disturbances.

Evidence for this model is derived from studies documenting a similar syndrome of hypercortisolism and cognitive decline in patients with Alzheimers disease (AD), and from studies conducted on aging and Brattleboro rats.

AD is a neurologic disease, characterized clinically by progressive loss of cognitive functions, and neuroanatomically by

pronounced degeneration of the nucleus basalis, the hippocampus, and the cerebral cortex. Selective neuronal loss in the hippocampus and cortex may underlie the cognitive deterioration observed in this disease (Coyle, Price, & DeLong, 1983). Of particular interest, though, is the finding of hypercortisolism and dexamethasone resistance in over 50% of patients with AD (Carnes, Smith, & Kalin, 1983). As in depression, the incidence of these HPA disturbances increases with advancing age (Greenwald, Mathe, Mohs, Levy, Johns, & Davis, 1987). Thus, similar to what has been observed in depressed patients, individuals with AD manifest both HPA dysregulation and cognitive deficits. A number of findings point to the hippocampus as the source of these disturbances.

First, data collected over a number of years, indicate that the hippocampus exerts inhibitory control over the HPA axis. In turn, glucocorticoids produced by the adrenals exert inhibitory action upon corticosteroid receptors located on neurons in the hippocampus (although much of the feedback inhibition does take place at the level of the pituitary and hypothalamus). For example (see Introduction), a number of experimental strategies (ablation, stimulation), measuring various indices of HPA activity (adrenal ascorbic acid depletion, urinary 17-OHCS, adrenal cortisol secretion), have shown that ablation of all or part of the hippocampus, or of its projections to the hypothalamus, produces a state of adrenocortical hyperactivity. Conversely, electrical stimulation of these structures inhibits HPA activity. More modern studies, employing more precise stimulation and ablation techniques, support the same conclusions (Dunn & Orr, 1984;

Silverman, Hoffman, & Zimmerman, 1981). In fact, ACTH is also hypersecreted in the aftermath of hippocampectomy, indicating that the hippocampus is mediating the inhibitory signal of circulating glucocorticoids (Wilson, Greer, Greer, & Roberts, 1980). This conclusion was drawn from the following evidence: after hippocampectomy, ACTH secretion was elevated compared to controls. Both groups were then adrenalectomized, and ACTH secretion increased to equally high concentrations in both conditions. Thus, in the absence of a glucocorticoid negative-feedback signal, the presence or absence of the hippocampus did not influence ACTH secretion.

Second, HPA dysregulation following hippocampal damage is manifest in a number of ways. Basal concentrations of cortisol have been reported to be elevated, either throughout the day, or during the circadian trough only (Fendler, Karmos, & Telegdy, 1961). The adrenal response to stress is heightened (Fendler, Karmos, & Telegdy, 1961), but moreover, there is an impaired ability to terminate the stress response (Sapolsky, Krey, & McEwen, 1983). These latter disturbances have been interpreted as representing disturbances in feedback mechanisms (Sapolsky, Krey, & McEwen, 1986), and in fact, hippocampal damage in rats produces dexamethasone resistance (Feldman & Conforti, 1980). Similar disturbances of HPA activity have been reported in depressed and AD patients.

A third line of evidence linking HPA dysregulation and cognitive deficits to hippocampal degeneration is derived from studies of Brattleboro rats and aging animals.

The Brattleboro rat is a strain congenitally lacking in

vasopressin (VP), due to the deletion of a single base from the DNA structure. These animals suffer from both endocrine and behavioral disturbances. VP apparently regulates concentrations of gluocorticoid receptors in the hippocampus, because the Brattleboro rat has a depletion of approximately 50% of these receptors. This loss of receptors is limited to the hippocampus. Additionally, certain aspects of memory and visual-spatial performance are disrupted in these rats. Both behavioral deficits (van Ree & de Wied, 1987) and hippocampal receptor numbers (Sapolsky, Krey, & McEwen, 1984) can be restored transiently by administration of VP or a centrally-acting VP analog. Sapolsky and colleagues (1984) have found that the Brattleboro rat hypersecretes glucocorticoids at the end of stress, and that this disturbance in feedback mechanisms is corrected with normalization of hippocampal glucocorticoid receptor concentrations following treatment with VP analogs. Cessation of treatment with VP results in a progressive decline in receptor numbers, and a reemergence of behavioral and feedback disturbances.

A similar, but less dramatic model, occurs naturally in the aging rat. During senescence in the male rat, hippocampal neurons are lost. This loss appears to occur progressively over the lifespan, so that by two years of age, approximately 10-20% of neurons in this region are lost. The damage that accompanies this loss is far more subtle than in the Brattleboro rats. These rats show cognitive deficits similar to the Brattleboro rats, but more critically, a well-documented syndrome of HPA dysregulation including elevated basal glucocorticoid (Landfield, Waymire, & Lynch, 1978) and ACTH concentrations (Tang &

Phillips, 1978), inability to terminate the stress response (Sapolsky, Krey, & McEwen, 1983), and resistance to feedback inhibition, whether induced by dexamethasone (Oxenkrug, McIntyre, Stanley, & Gershon, 1984), or naturally occuring corticosteroids (Sapolsky, Krey, & McEwen, 1986). Thus, the aging hippocampus is doubly impaired: with its loss of neurons and glucocorticoid receptors leading to a self-accelerating process of further hypercortisolism and neuronal death. Consequently, at some point, neuronal communication within and outside of the hippocampus becomes impeded, and such processes will become manifest as functional deficits.

These data suggest a number of implications regarding depression. First, certain depressive subtypes tend to be more strongly associated with HPA abnormalities than others. Next, stressors preceding or coincident with the depressive episode, may further dispose an individual to hypercortisolism and feedback disinhibition of the HPA axis. Finally, because the prevalence of cognitive impairment and HPA disturbances (UFC hypersecretion and dexamethasone resistance) become more pronounced with advanced age, these impairments may represent an interaction between normal involutional changes in the hippocampus (which, in humans, are usually below the threshold for disrupting endocrine function), and impairments attributable to the pathological condition.

This model is consistent with a number of the findings from the present study. First, it may explain why patients with the most subjective distress are nonsuppressors. Based on this model, the subjective distress associated with events antecedent to their

depression or with the depression per se may have produced elevation of basal cortisol levels. These excess glucocorticoids, in turn, would produce down-regulation of hippocampal glucocorticoid receptors, resulting in diminished sensitivity to circulating glucocorticoids, and ultimately a syndrome of cortisol hypersecretion. Second, it explains why HPA disturbances and cognitive impairments are more prominent in patients over 50 years of age (involutional hippocampal degeneration X effects of glucocorticoid excess related to depression). Third, it postulates a common denominator for both cognitive disturbance and HPA dysregulation. With this model I do not, however, purport to explain why patients become depressed, but rather why depressed patients manifest HPA dysregulation and cognitive impairment.

An additional, but less compelling explanation for the cognitive disturbances observed in states of HPA dysregulation, is derived from reports of reversible cerebral ventricular enlargement and sulcal prominence secondary to exogenous glucocorticoid therapy or Cushing's syndrome (Bentson, Reza, Winter, & Wilson, 1978; Heinz, Martinez, & Haenggeli, 1977; Okuno, Konishi, Yoshioka, & Nakano, 1980). Patients with anorexia nervosa also manifest similar cerebral atrophy (Heinz, Martinez, & Haenggeli, 1977), although it is not known whether this abnormality is related to the cortisol hypersecretion frequently observed in AN patients (Gerner & Gwirtsman, 1981). Recently, similar gross structural changes in the brain have been observed in CT scans from patients with affective illness (Kellner, Rubinow, Gold, & Post, 1983). Specifically, the ventricular-brain ratio (VBR), a measure of ventricular dilation, was significantly correlated with mean 24 hour

UFC in 10 depressed patients, independent of age. Moreover, the three patients with the largest VBRs were all HPA hypersecretors. Whether the apparent atrophy is reversible, and whether this atrophy is associated with cognitive deficits is not known. CT and pneumoencephalography data obtained from schizophrenic samples (Golden et al., 1980; Keilp et al., 1988), and from patients with various subcortical dementias (Adams & Victor, 1977) indicate that cerebral ventricular size is indeed correlated with cognitive impairment. However, studies conducted in other patient groups (e.g., steroid users, chronic alcoholics [note: alcoholism also reduces hippocampal neuron number]) have found no consistent relationship between increased VBR and intellectual performance. One possible explanation for this disparity is that the enlarged ventricles and cerebral atrophy present in the former groups represent an irreversible loss of cerebral tissue, whereas the reversible "atrophic" changes observed in the latter groups may be related to a shift of fluids occurring in the brain (over time), rather than actual loss of grey matter. Moreover, although the hypercortisolism of CS or following chronic ACTH administration seems to directly produce the ventricular enlargement observed in these patient groups, the cause and effect relationship in depressed patients remains largely speculative.

Future directions

A number of followup studies are planned or currently underway. One of the first questions that arises is whether the cognitive deficits noted in nonsuppressors are state-dependent (i.e., when

suppressor status reverts to normal with clinical remission, do these deficits persist?). Although I had originally proposed to investigate this issue when patients were discharged from the hospital, pilot data revealed that the anticholinergic side effects associated with antidepressant medications, and the cognitive sequelae associated with electroconvulsive therapy confounded the results of neuropsychological testing. Medication-free subjects from the original study are now being restudied (endocrine testing, neuropsychological assessment), at approximately 1 year following discharge. If the cognitive deficits originally noted are due to hippocampal neuronal degeneration, then initial DST nonsuppressors should continue to perform more poorly than initial suppressors. If, however, impairments are directly related to circulating levels of corticosteroids (and possible cerebral atrophy) during the depressive episode, then cognitive functioning should normalize, assuming that HPA functioning reverts to normal.

Another question that arises is whether heterogeneity of hormone profiles are related to variability in depressive and cognitive symptomatology in patients with other disturbances of the HPA axis. I am currently recruiting patients with various types of HPA dysregulation (e.g., Addison's disease [low cortisol, high ACTH], secondary adrenocortical insufficiency [low cortisol secondary to inadequate ACTH secretion], Cushing's syndrome of adrenal etiology [high cortisol, low ACTH], and Cushing's disease [hypercortisolism due to ACTH hypersecretion]), and patients receiving ACTH or corticosteroids as palliative therapy. Endocrine and cognitive assessments are being conducted longitudinally in order to assess the

effects of secondary metabolic complications (electrolyte disturbances, diabetes, hypertension, etc.) and to determine the sequence and chronology of change in response to normalization of endocrine function after treatment.

Finally, I will attempt to validate the derived discriminant function obtained in this study in a larger group of depressed patients. Beginning this fall, this study will be replicated as part of a federally-funded collaborative project with Hammersmith Laboratories and investigators from psychiatric research centers at Michigan State, UCLA, and the University of Iowa. In addition to measurements of UFC, which depend on complete 24-hour urine collection, a direct time-integrated measurement of free cortisol will be obtained from saliva, using a miniature diffusion-sink apparatus. This novel methodology may enable us to assess the degree to which brain exposure to biologically active cortisol (independently of other psycho-biological abnormalities of depression) may influence cognitive processes.

# CHAPTER 5

## SUMMARY

Several lines of evidence indicate that a relationship might exist between alterations in hypothalamic-pituitary-adrenocortical (HPA) activity and cognitive performance. First, circulating corticosteroids are known to have both direct and indirect effects on the central nervous system which could become manifest as functional disturbances. Second, disturbances in both mood and mentation have been reported in patients with Cushing's syndrome, a disorder characterized by sustained hypersecretion of adrenal corticosteroids. Third, exogenous glucocorticoids have been reported to impair both the acquisition and retention of conditioned avoidance responding in animals. Depressed patients represented an ideal group in which to explore the cognitive correlates of HPA dysregulation, because 50% of these patients show either cortisol hypersecretion and/or disturbances in the integrity of feedback mechanisms, without the presence of secondary metabolic complications.

The major objective of the present study was to elucidate further the relationship between HPA dysregulation and neuropsychological functioning in a group of depressed inpatients, using multiple indices of the endocrine system's activity and multiple measures of neuropsychological performance. Sixty patients admitted to the Payne Whitney Clinic, who met DSM-III criteria for major depressive disorder, participated in the study. Clinical assessment included the use of both diagnostic ratings and assessment of the symptom and severity

patterns of the patients' depression. Cognitive status was determined using an array of standard neuropsychological instruments. Both basal (plasma cortisol and ACTH, urinary free cortisol [UFC]) and provocative measures (dexamethasone suppression test [DST]) were used to identify biological subgroups of depressed patients. Hormone concentrations in blood and urine samples were measured using standard radioimmunoassay kits.

The main experimental hypothesis tested was that depressed patients with feedback abnormalities (DST nonsuppressors) would perform more poorly on certain neuropsychological tasks than depressed patients without measurable feedback disturbances (DST suppressors). Specifically, I speculated that visual-spatial, visual-ideational functions would be more severely compromised in the nonsuppressors. Further, because UFC excretion provides a better reflection of CNS exposure to active cortisol than individual plasma indices, a more robust association was expected between UFC levels and cognitive dysfunction than between any of the individual basal plasma indices and cognitive dysfunction. Finally, patients with high ACTH levels were expected to show more severe deterioration in cognitive functioning than those with lower ACTH levels.

The results of this study revealed that DST nonsuppressors were significantly more likely than suppressors to perform poorly on tests involving nonverbal memory, learning, manual dexterity, mental sequencing, abstract concept formation, and visual-spatial conceptualization. Moreover, nonsuppressors reported more subjective distress, had longer hospitalizations, and were more likely to receive

ECT than suppressors. These findings were independent of morning and evening levels of ACTH and pre-dexamethasone cortisol. Similar types of cognitive dysfunction were correlated with 24-hour excretion of UFC; however, the information obtained from UFC overlapped considerably with that obtained from dexamethasone suppression/nonsuppression of cortisol. In general, cognitive deficits appeared to be more strongly associated with the latter measure. HPA abnormalities and cognitive dysfunction were both related to age. The association between HPA abnormality and cognitive dysfunction, however, was shown to be independent of the effects of age.

Taken together, these findings suggest that cognitive disturbances are not byproducts of hypercortisolism per se. Rather, HPA activation and cognitive impairment appear to be downstream effects of a central disturbance. Recent studies point to the hippocampus as the likely locus of these perturbations. Because stressors antecedent to or coincident with a depressive episode cause the adrenals to secrete large amounts of cortisol, brain (in particular, hippocampal) exposure to glucocorticoids is increased. Cumulative exposure to elevated circulating levels of free cortisol has been shown to produce hippocampal neuronal death in animals, as well as down-regulation of hippocampal glucocorticoid receptors. These degenerative changes in hippocampal neurons and receptors can further compound the involutional changes that occur with advancing age, leading to a self-accelerating process of hypercortisolism, hippocampal neuronal death, and for those functions mediated by hippocampal activity, cognitive decline.

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# APPENDIX A

## Medical and Technical Factors Thay May Render DST Results Invalid

TABLE 1

FACTORS THAT MAY RENDER DST RESULTS INVALID

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Medical Factors

False-positive tests

- Pregnancy; high dose estrogens
- Cushing's disease or syndrome
- Profound weight loss; malnutrition; rigid dieting
- Hepatic enzyme induction (anticonvulsants [phenytoin, carbamazepine], sedative hypnotics [barbiturates, meprobamate, glutethimide, methaqualone, methyprylon])
- Major medical illnesses (congestive heart failure, advanced hepatic & renal disease, uncontrolled and ? controlled diabetes mellitus, ? AIDS, disseminated cancer)
- Alcohol or narcotics abuse; alcohol withdrawal
- ? Antidepressant/benzodiazepine withdrawal
- Physiological instability (fever, dehydration, severe nausea, trauma)
- ? Temporal lobe epilepsy
- ? Reserpine
- ? Alterations in activity rhythms (> 3 hr phase advance)

False-negative tests

- Hypopituitarism; Addison's disease
- Long-term synthetic steroid therapy
- Indomethacin; ? other nonsteroidal antiflammatory medications
- High-dose cyproheptadine
- ? High-dose benzodiazepines (>25 mg/day of diazepam)

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Technical Factors

- Patient compliance
- Plasma dexamethasone concentrations
- Acute behavioral stress
- Method of cortisol determination
- Cutoff criterion for nonsuppression

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APPENDIX B

Neuropsychological Tests Administered:

1. Vocabulary Subtest (WAIS-R)
2. Digit Span (WAIS-R)
3. Digit Symbol (WAIS-R)
4. Trail Making Test (Part A & B)
5. Rey Auditory Verbal Learning Test
6. Category Test (Sample item)
7. Stroop
8. Paced Auditory Serial Addition Test
9. Benton Visual Retention Test (Sample item)
10. Babcock Story Recall Test
11. Ammons Quick Test

Name _____ Date _____

VOCABULARY

| | SCORE |
|---|---|
| 1. Bed | _____ |
| 2. Ship | _____ |
| 3. Penny | _____ |
| 4. Winter | _____ |
| 5. Breakfast | _____ |
| 6. Repair | _____ |
| 7. Fabric | _____ |
| 8. Assemble | _____ |
| 9. Enormous | _____ |
| 10. Conceal | _____ |
| 11. Sentence | _____ |
| 12. Consume | _____ |

VOCABULARY

| | | SCORE |
|---|---|---|
| 13. | Regulate | ____ |
| 14. | Terminate | ____ |
| 15. | Commence | ____ |
| 16. | Domestic | ____ |
| 17. | Tranquil | ____ |
| 18. | Ponder | ____ |
| 19. | Designate | ____ |
| 20. | Reluctant | ____ |
| 21. | Obstruct | ____ |
| 22. | Sanctuary | ____ |
| 23. | Compassion | ____ |
| 24. | Evasive | ____ |

## VOCABULARY

| | SCORE |
|---|---|
| 25. Remorse | ____ |
| 26. Perimeter | ____ |
| 27. Generate | ____ |
| 28. Matchless | ____ |
| 29. Fortitude | ____ |
| 30. Tangible | ____ |
| 31. Plagiarize | ____ |
| 32. Ominous | ____ |
| 33. Encumber | ____ |
| 34. Audacious | ____ |
| 35. Tirade | ____ |
| TOTAL | ____ |

Name _____ Date _____

WEEK #1

**3. DIGIT SPAN** Discontinue after failure on BOTH TRIALS of any item. Administer BOTH TRIALS of each item, even if subject passes first trial.

| DIGITS FORWARD | | Pass-Fail | Score 2, 1, or 0 |
|---|---|---|---|
| 1. | 5 - 8 - 2 | | |
| | 6 - 9 - 4 | | |
| 2. | 6 - 4 - 3 - 9 | | |
| | 7 - 2 - 6 - 8 | | |
| 3. | 4 - 2 - 7 - 3 - 1 | | |
| | 7 - 5 - 6 - 3 - 8 | | |
| 4. | 6 - 1 - 9 - 4 - 7 - 3 | | |
| | 3 - 9 - 2 - 4 - 8 - 7 | | |
| 5. | 5 - 9 - 1 - 7 - 4 - 2 - 8 | | |
| | 4 - 1 - 7 - 9 - 3 - 8 - 6 | | |
| 6. | 5 - 8 - 1 - 9 - 2 - 8 - 4 - 7 | | |
| | 3 - 8 - 2 - 9 - 5 - 1 - 7 - 4 | | |
| 7. | 2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4 | | |
| | 7 - 1 - 3 - 9 - 4 - 2 - 5 - 8 - 6 | | |
| | *Total Forward* | | Max=14 |

| DIGITS BACKWARD* | | Pass-Fail | Score 2, 1, or 0 |
|---|---|---|---|
| 1. | 2 - 4 | | |
| | 5 - 8 | | |
| 2. | 8 - 2 - 9 | | |
| | 4 - 1 - 6 | | |
| 3. | 3 - 2 - 7 - 9 | | |
| | 4 - 9 - 6 - 8 | | |
| 4. | 1 - 6 - 2 - 8 - 6 | | |
| | 8 - 1 - 8 - 4 - 3 | | |
| 5. | 5 - 3 - 8 - 4 - 1 - 8 | | |
| | 7 - 2 - 4 - 8 - 6 - 8 | | |
| 6. | 8 - 1 - 2 - 8 - 3 - 8 - 5 | | |
| | 4 - 7 - 3 - 9 - 1 - 2 - 8 | | |
| 7. | 8 - 4 - 3 - 7 - 8 - 2 - 5 - 8 | | |
| | 7 - 2 - 8 - 1 - 9 - 6 - 8 - 3 | | |
| | *Total Backward* | | Max=14 |

*Administer DIGITS BACKWARD even if subject scores 0 on DIGITS FORWARD.

[ ] Forward + [ ] Backward = [ ] Total (Max=28)

Date _____

WEEK #2

**3. DIGIT SPAN** Discontinue after failure on BOTH TRIALS of any item. Administer BOTH TRIALS of each item, even if subject passes first trial.

| DIGITS FORWARD | | Pass-Fail | Score 2, 1, or 0 |
|---|---|---|---|
| 1. | 5 - 6 - 2 | | |
| | 6 - 9 - 4 | | |
| 2. | 6 - 4 - 3 - 9 | | |
| | 7 - 2 - 6 - 6 | | |
| 3. | 4 - 2 - 7 - 3 - 1 | | |
| | 7 - 5 - 6 - 3 - 8 | | |
| 4. | 6 - 1 - 9 - 4 - 7 - 3 | | |
| | 3 - 9 - 2 - 4 - 6 - 7 | | |
| 5. | 5 - 9 - 1 - 7 - 4 - 2 - 8 | | |
| | 4 - 1 - 7 - 9 - 3 - 6 - 6 | | |
| 6. | 5 - 8 - 1 - 9 - 2 - 8 - 4 - 7 | | |
| | 3 - 6 - 2 - 9 - 5 - 1 - 7 - 4 | | |
| 7. | 2 - 7 - 5 - 6 - 8 - 2 - 5 - 8 - 4 | | |
| | 7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8 | | |
| | *Total Forward* | | Max=14 |

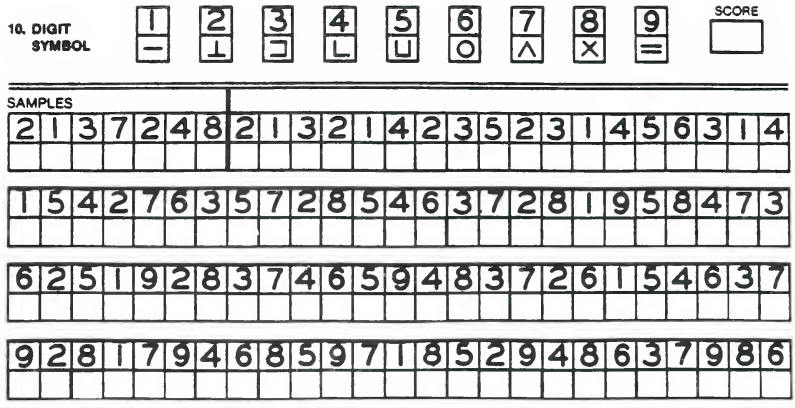
| DIGITS BACKWARD* | | Pass-Fail | Score 2, 1, or 0 |
|---|---|---|---|
| 1. | 2 - 4 | | |
| | 5 - 8 | | |
| 2. | 8 - 2 - 9 | | |
| | 4 - 1 - 5 | | |
| 3. | 3 - 2 - 7 - 8 | | |
| | 4 - 6 - 8 - 8 | | |
| 4. | 1 - 5 - 2 - 8 - 8 | | |
| | 8 - 1 - 8 - 4 - 3 | | |
| 5. | 5 - 3 - 8 - 4 - 1 - 8 | | |
| | 7 - 2 - 4 - 8 - 6 - 8 | | |
| 6. | 8 - 1 - 2 - 8 - 3 - 8 - 5 | | |
| | 4 - 7 - 3 - 8 - 1 - 2 - 8 | | |
| 7. | 9 - 4 - 3 - 7 - 8 - 2 - 5 - 8 | | |
| | 7 - 2 - 8 - 1 - 8 - 8 - 5 - 3 | | |
| | *Total Backward* | | Max=14 |

*Administer DIGITS BACKWARD even if subject scores 0 on DIGITS FORWARD.

[ ] Forward + [ ] Backward = [ ] Total (Max=28)

Name _____ Date _____

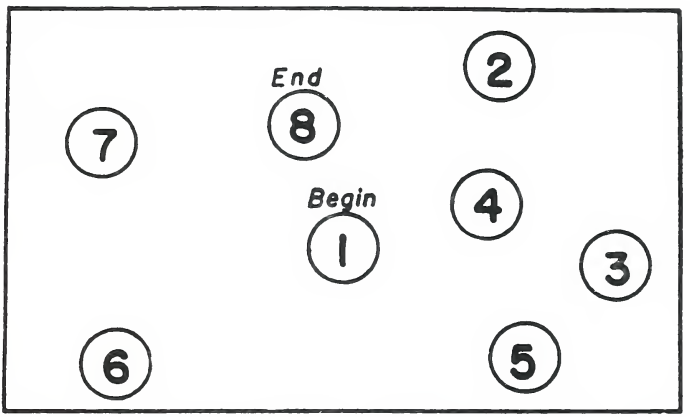
DIGIT SYMBOL - WEEK #1



# TRAIL MAKING

## Part A

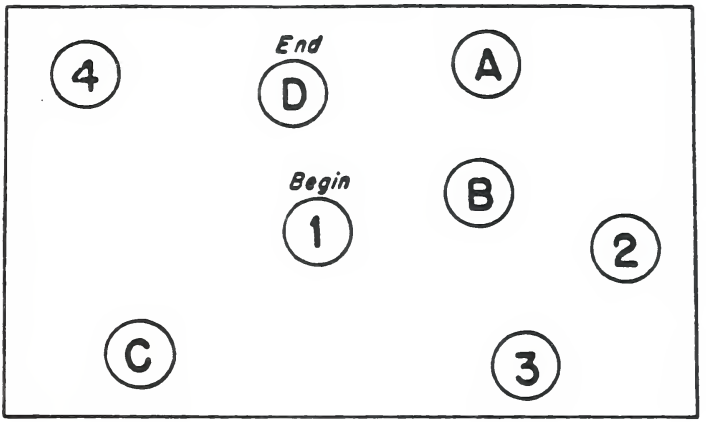
SAMPLE



# TRAIL MAKING

## Part B

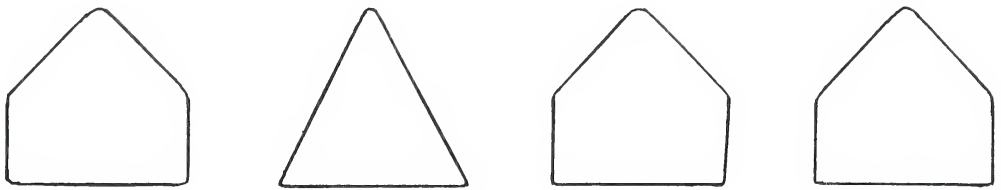
SAMPLE



Rey Auditory-Verbal Learning Test (AVLT)

| List A | List B | List C |
|---|---|---|
| Drum | Desk | Book |
| Curtain | Ranger | Flower |
| Bell | Bird | Train |
| Coffee | Shoe | Rug |
| School | Stove | Meadow |
| Parent | Mountain | Harp |
| Moon | Glasses | Salt |
| Garden | Towel | Finger |
| Hat | Cloud | Apple |
| Farmer | Boat | Chimney |
| Nose | Lamb | Button |
| Turkey | Gun | Key |
| Color | Pencil | Dog |
| House | Church | Glass |
| River | Fish | Rattle |

| List D | List E |
|---|---|
| Musician | Violin |
| Bridge | Tree |
| Master | Tie |
| Bread | Ham |
| Wall | Suitcase |
| Pebbles | Cousin |
| Peel | Ear |
| Teeth | Knife |
| Field | Staircase |
| Forest | Dog |
| Gun | Banana |
| Shoulder | Tool |
| Hand | Hunter |
| Hat | Bucket |
| Song | Champagne |



SAMPLE ITEM: CATEGORY TEST

| | | | | |
|---|---|---|---|---|
| RED | BLUE | GREEN | RED | BLUE |
| GREEN | GREEN | RED | BLUE | GREEN |
| BLUE | RED | BLUE | GREEN | RED |
| GREEN | BLUE | RED | RED | BLUE |
| RED | RED | GREEN | BLUE | GREEN |
| BLUE | GREEN | BLUE | GREEN | RED |
| RED | BLUE | GREEN | BLUE | GREEN |
| BLUE | GREEN | RED | GREEN | RED |
| GREEN | RED | BLUE | RED | BLUE |
| BLUE | GREEN | GREEN | BLUE | GREEN |
| GREEN | RED | BLUE | RED | RED |
| RED | BLUE | RED | GREEN | BLUE |
| GREEN | RED | BLUE | RED | GREEN |
| BLUE | BLUE | RED | GREEN | RED |
| RED | GREEN | GREEN | BLUE | BLUE |
| BLUE | BLUE | RED | GREEN | RED |
| RED | GREEN | BLUE | RED | GREEN |
| GREEN | RED | GREEN | BLUE | BLUE |
| RED | BLUE | RED | GREEN | RED |
| GREEN | RED | GREEN | BLUE | GREEN |

*** PASAT -*** FORM A *** RATE: 2.4 2.0 1.6 1.2

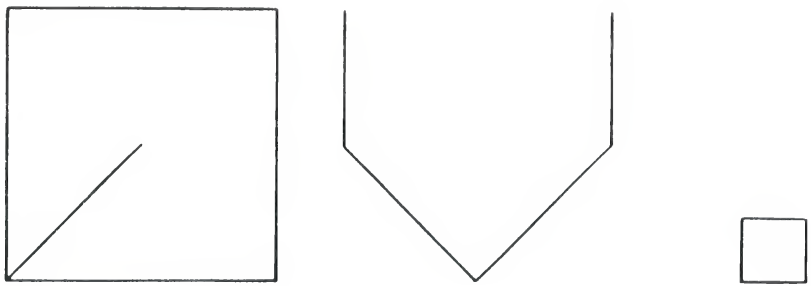
Patient Name: _____ Date: _____

* FORM A - PASAT - FORM A *

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | | -- | | | | | | |
| 2 | | 3 | 5 | | 9 | 8 | | 9 |
| 9 | | 11 | 6 | | 11 | 3 | | 11 |
| 6 | | 15 | 2 | | 8 | 1 | | 4 |
| 3 | | 9 | 9 | | 11 | 7 | | 8 |
| 4 | | 7 | 3 | | 12 | 3 | | 10 |
| 5 | | 9 | 8 | | 11 | 6 | | 9 |
| 2 | | 7 | 6 | | 14 | 5 | | 11 |
| 6 | | 8 | 9 | | 15 | 2 | | 7 |
| 9 | | 15 | 1 | | 10 | 3 | | 5 |
| 1 | | 10 | 7 | | 8 | 8 | | 11 |
| 6 | | 7 | 9 | | 16 | 1 | | 9 |
| 8 | | 14 | 4 | | 13 | 3 | | 4 |
| 1 | | 9 | 1 | | 5 | 8 | | 11 |
| 6 | | 7 | 6 | | 7 | 4 | | 12 |
| 8 | | 14 | 3 | | 9 | 7 | | 11 |
| 4 | | 12 | 8 | | 11 | 8 | | 15 |
| 9 | | 13 | 9 | | 17 | 3 | | 11 |
| 3 | | 12 | 4 | | 13 | 4 | | 7 |
| 2 | | 5 | 2 | | 6 | 2 | | 6 |
| 4 | | 6 | 1 | | 3 | 6 | | 8 |

[H. Crovitz & F. Schmitt]

COMMENTS:



SAMPLE ITEM: BENTON VISUAL RETENTION TEST

BABCOCK STORY RECALL TEST

Instructions: "I am going to read a short paragraph to you. Listen carefully to what I am reading. I will ask you to repeat it."

1 2 3 4 5 6
"December 6. Last week a river overflowed in a small town ten miles from

7 8 9 10
Albany. Water covered the streets and entered the houses. Fourteen persons were

11 12 13 14 15
drowned, and 600 persons caught cold because of the dampness and cold weather.

16 17 18 19 20 21
In saving a boy who was caught under a bridge, a man cut his hands."

Immediate Recall: "Now begin at the beginning and tell me all you can remember."

# units recalled _____ # of confabulations_____

After recall: "In a little while I'm going to ask you to tell me how much of the story you can still remember. I am going to read the story to you again now so that you'll have it fresh in your memory for the next time."

Delayed Recall: (Obtained after 20 minutes of testing involving verbal material)

# of units recalled_____ # of confabulations_____

Scoring: 1 point per unit underlined + 4 added to Immediate Recall score.

# QUICK TEST

R. B. Ammons and C. H. Ammons

Top of Card

Answer Alternatives
(key to left of items)




| FORM 1 | | FORM 2 | | FORM 3 | |
|---|---|---|---|---|---|
| 4 belt (easy) | | 2 cans (easy) | | 2 sheet (easy) | |
| 1 dancing (easy) | | 3 chewing (easy) | | 1 exercise (easy) | |
| 4 traffic (easy) | | 4 falling (easy) | | 2 machine (easy) | |
| 4 whistle (easy) | | 3 dinner (easy) | | 4 burners (easy) | |
| 3 fence (easy) | 5 | 1 cow (easy) | 5 | 1 audience (easy) | |
| 2 drink (easy) | | 2 groceries (easy) | | 3 dish (easy) | |
| 3 wreck (easy) | | 4 hat (easy) | | 2 drying (easy) | |
| 1 music (easy) | | 3 sitting (easy) | | 3 food (easy) | |
| 2 medicine (easy) | | 1 country (easy) | | 3 fork (easy) | |
| 4 gun (easy) | 10 | 4 danger (easy) | 10 | 1 crowd (easy) | |
| 2 pepper (easy) | | 3 plate (easy) | | 3 slice (easy) | |
| 3 racing (easy) | | 1 river (easy) | | 2 washing (easy) | |
| 2 salt (easy) | | 3 tasting (easy) | | 4 tears (easy) | |
| 1 woman (easy) | | 2 shelves (easy) | | 1 fighting (easy) | |
| 2 sugar (easy) | 15 | 1 sky (easy) | 15 | 4 kitchen (easy) | |
| 3 track (easy) | | 3 table (easy) | | 3 tasty (easy) | |
| 4 school (6) | | 4 carelessness (6) | | 2 windy (6) | |
| 1 partner (6) | | 3 manners (6) | | 4 pitiful (6) | |
| 1 couples (7) | | 2 adding (7) | | 1 contest (7) | |
| 3 rail (7) | 20 | 4 injury (7) | 20 | 4 sorrow (8) | |
| 4 respectful (8) | | 2 merchandise (8) | | 1 loser (7) | |
| 3 betting (8) | | 3 waitress (8) | | 4 heartbreak (8) | |
| 3 daring (9) | | 1 horizon (9) | | 1 struggle (9) | |
| 3 stadium (9) | | 2 retail (9) | | 2 rotary (10) | |
| 4 pedestrian (10) | 25 | 1 irrigation (10) | 25 | 1 opponents (9) | |
| 1 graceful (10) | | 4 unaware (10) | | 4 grief (10) | |
| 2 fluid (11) | | 1 current (11) | | 3 utensils (11) | |
| 2 solution (11) | | 1 fertile (11) | | 2 lever (11) | |
| 4 discipline (12) | | 4 descending (12) | | 3 portion (12) | |
| 3 bleachers (12) | 30 | 1 spacious (12) | 30 | 3 edible (12) | |
| 2 crystallized (13) | | 2 proprietor (13) | | 1 exhibition (13) | |
| 1 turntable (13) | | 4 inattentive (13) | | 4 soothed (13) | |
| 2 saccharin (14) | | 3 indulging (14) | | 4 caress (14) | |
| 4 immature (14) | | 1 precipitation (14) | | 1 combatant (14) | |
| 1 cordiality (15) | 35 | 1 freshet (15) | 35 | 4 forlorn (15) | |
| 3 velocity (15) | | 4 transom (15) | | 3 nutrient (15) | |
| 4 decisive (16) | | 3 consumption (16) | | 4 solace (16) | |
| 3 laceration (16) | | 1 aquatic (16) | | 1 pacify (16) | |
| 3 foliage (17) | | 4 perilous (17) | | 1 contorted (17) | |
| 4 imperative (17) | 40 | 1 terrain (17) | 40 | 4 jest (17) | |
| 1 intimacy (18) | | 4 imminent (18) | | 4 doleful (18) | |
| 2 concoction (18) | | 2 foresight (18) | | 3 tines (18+) | |
| 1 conviviality (18+) | | 1 condensation (18+) | | 4 disconsolate (18) | |
| 4 chevrons (18+) | | 3 satiation (hard) | | 3 sustenance (18+) | |
| 2 condiment (hard) | 45 | 3 visceral (hard) | 45 | 4 maudlin (hard) | |
| 3 cacophony (hard) | | 1 bovine (18+) | | 3 gustatory (hard) | |
| 2 miscible (hard) | | 3 replete (hard) | | 4 poignant (hard) | |
| 2 imbibe (hard) | | 3 prehension (hard) | | 1 bellicose (hard) | |
| 1 amicable (hard) | | 4 ingress (hard) | | 3 comestible (hard) | |
| 2 pungent (hard) | 50 | 3 celerity (hard) | 50 | 4 despondency (hard) | |

Score _____ _____ _____



QT

Name: _____ Age: ___ Sex: M F Date: _____ Tester: _____

1 2 3 4

Form: 1 2 3 1+2 1+3 2+3 1+2+3 : Form

Performance: Raw Score: _____ _____ _____ _____ _____ _____ _____ : Raw Score

MA: _____ _____ _____ _____ _____ _____ _____ : MA

IQ: _____ _____ _____ _____ _____ _____ _____ : IQ

Percentile: _____ _____ _____ _____ _____ _____ _____ : Percentile

Notes: _____

## APPENDIX C

Impairment Criteria for Selected Neuropsychological Tests:

1. Trail-Making Test
2. Purdue Pegboard
3. Babcock Story Recall Test
4. Rey Auditory Verbal Learning Test
5. Benton Visual Retention Test
6. Symbol Digit Modalities Test

TABLE 3

IMPAIRMENT CRITERIA FOR SELECTED NEUROPSYCHOLOGICAL TESTS

**TRAIL-MAKING TEST**

| AGE | 20 to 39 | | 40 to 49 | | 50 to 59 | | 60 to 69 | | 70 to 79 | |
|---|---|---|---|---|---|---|---|---|---|---|
| PART | A | B | A | B | A | B | A | B | A | B |
| TIME > | 42 | 94 | 45 | 100 | 49 | 135 | 67 | 172 | 105 | 292 |

**PURDUE PEGBOARD**

| AGE | UNDER AGE 60 | 60 AND OLDER |
|---|---|---|
| PREFERRED HAND | <13 | <10 |
| NON-PREFERRED HAND | <11 | <10 |
| SIMULTANEOUS | <10 | < 8 |

**BABCOCK STORY RECALL TEST**

| IQ | AVERAGE (90-109) | HIGH AVERAGE (110-119) | SUPERIOR (120-129) |
|---|---|---|---|
| IMMEDIATE | ≤12 | ≤12 | ≤13 |
| DELAYED | ≤13 | ≤16 | ≤15 |

## REY AVLT

| AGE | TRIAL 1 | TRIAL 5 | (RECALL) TRIAL 7 | RECOG | (LEARNING) TRIAL 5-1 |
|---|---|---|---|---|---|
| 0-49 | 4 | 9 | 7 | 11 | 5 |
| 50-59 | 3 | 7 | 5 | 9 | 4 |
| 60-69 | 3 | 5 | 3 | 7 | 3 |
| 70 + | 2 | 4 | 3 | 6 | 2 |

## BENTON VISUAL RETENTION TEST

TOTAL NUMBER CORRECT

| AGE | 15-44 | 45-54 | 55-64 |
|---|---|---|---|
| IQ ≥110 | ≤7 | ≤6 | ≤5 |
| 95 - 109 | ≤6 | ≤5 | ≤4 |
| 80 - 94 | ≤5 | ≤4 | ≤3 |
| 70 - 79 | ≤4 | ≤3 | ≤2 |

TOTAL NUMBER OF ERRORS

| AGE | 15-39 | 40-54 | 55-59 | 60-64 |
|---|---|---|---|---|
| IQ ≥110 | ≥5 | ≥6 | ≥7 | ≥8 |
| 105-109 | ≥6 | ≥7 | ≥8 | ≥9 |
| 95-104 | ≥7 | ≥8 | ≥9 | ≥10 |
| 90-94 | ≥8 | ≥9 | ≥10 | ≥11 |
| 80-89 | ≥9 | ≥10 | ≥11 | ≥12 |
| 70-79 | ≥10 | ≥11 | ≥12 | ≥13 |

## SYMBOL DIGIT MODALITIES TEST

| AGE | 18-24 | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 |
|---|---|---|---|---|---|---|
| SCORE < | 48 | 47 | 43 | 38 | 33 | 26 |

# APPENDIX D

## DSM-III Criteria for Major Depressive Episode

TABLE 2

DSM-III CRITERIA FOR MAJOR DEPRESSIVE EPISODE

---

A. Dysphoric mood or loss of pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood.

B. At least four of the following symptoms have been present nearly every day for a period of at least two weeks:

(1) poor appetite or significant weight loss or increased appetite or significant weight gain
(2) insomnia or hypersomnia
(3) psychomotor agitation or retardation
(4) loss of interest or pleasure in usual activities, or decrease in sex drive
(5) loss of energy; fatigue
(6) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt
(7) complaints or evidence of inability to think or concentrate
(8) recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt

C. Neither of the following dominate the clinical picture when an affective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it has remitted:

(1) preoccupation with a mood-incongruent delusion or hallucination
(2) bizarre behavior

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder.

E. Not due to any Organic Mental Disorder or Uncomplicated Bereavement.

---

# APPENDIX E

Clinical Assessment Instruments:

1. Criteria for Determining Endogenicity
2. Hamilton Depression Rating Scale
3. Global Assessment Scale
4. Beck Depression Inventory
5. Raskin Mood Scale

CRITERIA FOR DETERMINING ENDOGENICITY

| Clinical Item | Weight | Scoring Range |
|---|---|---|
| Decreased appetite * | 9 | 0-2 |
| Guilt * | 6 | 0-4 |
| Agitation * | 4 | 0-4 |
| Delusions (Affective) | 3 | 0-8 |
| Work and interests * | 3 | 0-4 |
| Retardation * | 2 | 0-4 |
| Loss of pleasure | 2 | 0-2 |
| Precipitants present | - 6 | 0-1 |

Scoring: The DI score for a given patient is the sum of that patient's scores on the 8 clinical items multiplied by the appropriate item weights. A score of >26 is considered to be definitely endogenous, between 19 and 26 is indeterminant, and <19 is nonendogenous. The items with asterisks are rated according to the Hamilton Depression Rating Scale item, from which they were taken. The Delusions item is comprised of 4 sub-items: delusions of guilt, delusions of poverty, hypochondriacal delusions, and delusions of hopelessness. Each sub-item is scored from 0-2 points, with 0 = absent, 1 = overvalued ideas amenable to reason, and 2 = fixed delusion. Total score (before weighting) can be as high as 8. Precipitants are marked as present or absent and subtracted from the other scores.

NAME _____ DATE _____

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION

Card 01 (1-2) Subject's ID No. Study (7-8)

Facility Number | Number in Study | Date

Initials of Subject _____ (3) (4-6)

Day in Study (9-10) Actual No. of days Since Admission (11-12) Rater No. (13-14)

Type of Rating 15 Video No. 16

(Live=1; Video=2)

Instructions: For each item, circle the number to the left of the "cue" which best characterizes the patient.

| Col. | |
|---|---|
| T2T | 1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)<br>0 Absent<br>1 These feeling states indicated only on questionning<br>2 These feeling states spontaneously reported verbally<br>3 Communicates feeling states non-verbally, i.e., through facial expression, posture, voice, and tendency to weep<br>4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication |
| T22 | 2. FEELINGS OF GUILT<br>0 Absent<br>1 Self-reproach, feels he has let people down<br>2 Ideas of guilt or rumination over past errors or sinful deeds<br>3 Present illness is a punishment. Delusions of guilt<br>4 Hears accusary or denunciatory voices and/or experiences threatening visual hallucinations |
| T23 | 3. SUICIDE<br>0 Absent<br>1 Feels life is not worth living<br>2 Wishes he were dead or any thoughts of possible death to self<br>3 Suicide ideas or gesture<br>4 Attempts at suicide (any serious attempt rates 4) |
| T24 | 4. INSOMNIA EARLY<br>0 No difficulty falling asleep<br>1 Complains of occasional difficulty falling asleep, i.e., more than 1/2 hour<br>2 Complains of nightly difficulty falling asleep |
| T25 | 5. INSOMNIA MIDDLE<br>0 No difficulty<br>1 Patient complains of being restless and disturbed during the night<br>2 Waking during the night -- any getting out of bed rates 2 (except for purposes of voiding) |

Rater No._____ Date_____

Col. 126

6. INSOMNIA LATE
- 0 No difficulty
- 1 Waking in early hours of the morning but goes back to sleep
- 2 Unable to fall asleep again if gets out of bed

Col. 127

7. WORK AND ACTIVITIES
- 0 No difficulty
- 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
- 2 Loss of interest in activity, hobbies, or work -- either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
- 3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
- 4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform chores unassisted

Col. 128

8. RETARDATION (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
- 0 Normal speech and thought
- 1 Slight retardation at interview
- 2 Obvious retardation at interview
- 3 Interview difficult
- 4 Complete stupor

Col. 129

9. AGITATION
- 0 None
- 1 "Playing with" hands, hair, etc.
- 2 Hand-wringing, nail-biting, hair-pulling, biting of lips

Col. 130

10. ANXIETY PSYCHIC
- 0 No difficulty
- 1 Subjective tension and irritability
- 2 Worrying about minor matters
- 3 Apprehensive attitude apparent in face and speech
- 4 Fears expressed without questionning

Col. 131

11. ANXIETY SOMATIC
- 0 Absent
- 1 Mild
- 2 Moderate
- 3 Severe
- 4 Incapacitating

Physiological concomitants of anxiety such as: Gastrointestinal: Dry mouth, wind, indigestion, diarrhea, cramps, belching. Cardiovascular: Palpitations, headaches. Respiratory: Hyperventilation, sighing. Urinary frequency. Sweating

Col. 132

12. SOMATIC SYMPTOMS GASTROINTESTINAL
- 0 None
- 1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
- 2. Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for G.I. symptoms

Col.

13. SOMATIC SYMPTOMS GENERAL
- 0 None
- 1 Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability
- 2 Any clear-cut symptom rates 2

133

14. GENITAL SYMPTOMS
- 0 Absent
- 1 Mild
- 2 Severe
- 9 Not ascertained

Symptoms such as: Loss of libido, Menstrual disturbances

134

15. HYPOCHONDRIASIS
- 0 Not present
- 1 Self-absorption (bodily)
- 2 Preoccupation with health
- 3 Frequent complaints, requests for help, etc.
- 4 Hypochondriacal delusions

135

16. LOSS OF WEIGHT

A. WHEN RATING BY HISTORY
- 0 No weight loss
- 1 Probable weight loss associated with present illness
- 2 Definite (according to patient) weight loss

B. ON WEEKLY RATINGS BY WARD PSYCHIATRIST, WHEN ACTUAL WEIGHT CHANGES ARE MEASURED
- 0 Less than 1 lb. weight loss in week
- 1 Greater than 1 lb. weight loss in week
- 2 Greater than 2 lb. weight loss in week

136

17. INSIGHT
- 0 Acknowledges being depressed and ill
- 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2. Denies being ill at all

137

18. DIURNAL VARIATION

| A.M. | P.M. | |
|---|---|---|
| 0 | 0 | Absent |
| 1 | 1 | Mild |
| 2 | 2 | Severe |

If symptoms are worse in the morning or evening, note which it is and rate severity of variation

138

19. DEPERSONALIZATION AND DEREALIZATION
- 0 Absent
- 1 Mild
- 2 Moderate
- 3 Severe
- 4 Incapacitating

Such as: Feelings of unreality, Nihilistic ideas

139

Rater No._____ Date_____

Col.

20. PARANOID SYMPTOMS
0 None
1)
2) Suspicious
3 Ideas of reference
4 Delusions of reference and persecution

140

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS
0 Absent
1 Mild
2 Severe

141

22. HELPLESSNESS
0 Not present
1 Subjective feelings which are elicited only by inquiry
2 Patient volunteers his helpless feelings
3 REQUIRES urging, guidance and reassurance to accomplish ward chores or personal hygiene
4 Requires physical assistance for dress, grooming, eating, bedside tasks or personal hygiene

142

23. HOPELESSNESS
0 Not present
1 Intermittently doubts that "things will improve" but can be reassured
2 Consistently feels "hopeless" but accepts reassurances
3 Expresses feelings of discouragement, despair, pessimism about future, which cannot be dispelled
4 Spontaneously and inappropriately perseverates, "I'll never get well," or its equivalent

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24. WORTHLESSNESS
0 Not present
1 Indicates feelings of worthlessness (loss of self-esteem) only on questioning
2 Spontaneously indicates feelings of worthlessness (loss of self-esteem)
3 Different from 2 by degree: Patient volunteers that he is "no good," "inferior," etc.
4 Delusional notions of worthlessness -- i.e., "I am a heap of garbage" or its equivalent

Ranges from mild loss of esteem, feelings of inferiority, self-depreciation to delusional notions of worthlessness

144

11
179-180

PATIENT NAME _____ DATE _____

SADS-C

GLOBAL ASSESSMENT SCALE. Rate the subject's lowest level of functioning for the past week. Use intermediary levels when appropriate (e.g., 35, 58, 62). Rate actual functioning regardless of treatment or prognosis.

..... GAS Rating

244–245

100 | 91 Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his warmth and integrity. No Symptoms.

90 | 81 Good functioning in all areas, many interests, socially effective, generally satisfied with life. There may or may not be transient symptoms and "everyday" worries that only occasionally get out of hand.

80 | 71 No more than slight impairment in functioning, varying degrees of "everyday" worries and problems that sometimes get out of hand. Minimal symptoms may or may not be present.

70 | 61 Some mild symptoms (e.g., depressive mood and mild insomnia) OR some difficulty in several areas of functioning, but generally functioning pretty well, has some meaningful interpersonal relationships and most untrained people would not consider him "sick."

60 | 51 Moderate symptoms OR generally functioning with some difficulty (e.g., few friends and flat affect, depressed mood and pathological self-doubt, euphoric mood and pressure of speech, moderately severe antisocial behavior).

50 | 41 Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (e.g., suicidal preoccupation or gesture, severe obsessional rituals, frequent anxiety attacks, serious antisocial behavior, compulsive drinking, mild but definite manic syndrome).

40 | 31 Major impairment in several areas, such as work, family relations, judgment, thinking or mood (e.g., depressed woman avoids friends, neglects family, unable to do housework), OR some impairment in reality testing or communication (e.g., speech is at times obscure, illogical or irrelevant), OR single suicide attempt.

30 | 21 Unable to function in almost all areas (e.g., stays in bed all day) OR behavior is considerably influenced by either delusions or hallucinations OR serious impairment in communication (e.g., sometimes incoherent or unresponsive )or judgment (e.g., acts grossly inappropriately).

20 | 11 Needs some supervision to prevent hurting self or others, or to maintain minimal personal hygiene (e.g., repeated suicide attempts, frequently violent, manic excitement, smears feces), OR gross impairment in communication (e.g., largely incoherent or mute).

10 | 1 Needs constant supervision for several days to prevent hurting self or others (e.g., requires an intensive care unit with special observation by staff), makes no attempt to maintain minimal personal hygiene, or serious suicide act with clear intent and expectation of death.

MOOD SCALE

Name _____ Date _____ Time _____

Rate yourself on each word or phrase, by finding the column which best describes how you feel today. Then place a check mark (✓ ) in one of the four boxes to show this. BE SURE TO ONLY RATE YOUR MOOD BASED ON THE WAY YOU ARE FEELING TODAY.

| MOOD | NOT AT ALL | A LITTLE | QUITE A BIT | EX-TREMELY |
|---|---|---|---|---|
| 1. Sad | | | | |
| 2. Tense | | | | |
| 3. Angry | | | | |
| 4. Happy | | | | |
| 5. Relaxed | | | | |
| 6. Good-natured | | | | |
| 7. Tired | | | | |
| 8. Full of pep | | | | |
| 9. Confused | | | | |
| 10. Able to think clearly | | | | |
| 11. Down-hearted | | | | |
| 12. On edge | | | | |
| 13. Irritable | | | | |
| 14. Carefree | | | | |
| 15. At ease | | | | |
| 16. Friendly | | | | |
| 17. Worthless | | | | |
| 18. Sleepy | | | | |
| 19. Active | | | | |
| 20. Forgetful | | | | |
| 21. Able to concentrate | | | | |
| 22. Unhappy | | | | |
| 23. Anxious | | | | |
| 24. Impatient | | | | |

| MOOD | NOT AT ALL | A LITTLE | QUITE A BIT | EX-TREMELY |
|---|---|---|---|---|
| 25. Cheerful | | | | |
| 26. Satisfied | | | | |
| 27. Kind | | | | |
| 28. Useless | | | | |
| 29. Worn out | | | | |
| 30. Lively | | | | |
| 31. Efficient | | | | |
| 32. Depressed | | | | |
| 33. Restless | | | | |
| 34. Annoyed | | | | |
| 35. Dependable | | | | |
| 36. Troubled by conscience | | | | |
| 37. Weary | | | | |
| 38. Alert | | | | |
| 39. Blue | | | | |
| 40. Nervous | | | | |
| 41. Rude | | | | |
| 42. Regretful | | | | |
| 43. Troubled | | | | |
| 44. Jittery | | | | |
| 45. Sarcastic | | | | |
| 46. Warm-hearted | | | | |
| 47. Ashamed | | | | |
| 48. Worried | | | | |
| 49. Pleasant | | | | |

| MOOD | NOT AT ALL | A LITTLE | QUITE A BIT | EX-TREMELY |
|---|---|---|---|---|
| 50. Lonely | | | | |
| 51. Able to work | | | | |
| 52. Consid-erate | | | | |

## BECK INVENTORY

Name _____ Date _____

This is a questionnaire. On the questionnaire are groups of statements. Please read all of the statements in that group which best describes the way you feel today. Circle the number of the statement you have chosen. If several statements in the group seem to apply equally well, circle each one.

Be sure to read all the statements in each group before making your choice.

A. 0 I do not feel sad
1 I feel sad
2 I am sad all the time and I can't snap out of it
3 I am so sad or unhappy that I can't stand it

B. 0 I am not particularly discouraged about the future
1 I feel discouraged about the future
2 I feel I have nothing to look forward to
3 I feel that the future is hopeless and things cannot improve

C. 0 I do not feel like a failure
1 I feel I have failed more than the average person
2 As I look back on my life all I can see is a lot of failures
3 I feel I am a complete failure as a person

D. 0 I get as much satisfaction out of things as I used to
1 I don't enjoy things the way I used to
2 I don't get real satisfaction out of anything any more
3 I am dissatisfied or bored with everything

E. 0 I don't feel particularly guilty
1 I feel guilty a good part of the time
2 I feel quite guilty most of the time
3 I feel guilty all of the time

F. 0 I don't feel I am being punished
1 I feel I may be punished
2 I expect to be punished
3 I feel I am being punished

G. 0 I don't feel disappointed in myself
1 I am disappointed in myself
2 I am disgusted with myself
3 I hate myself

H. 0 I don't feel I am any worse than anyone else
1 I am critical of myself for my weaknesses and mistakes
2 I blame myself all the time for my faults
3 I blame myself for everything bad that happens

I. 0 I don't have any thoughts of killing myself
1 I have thoughts of killing myself but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

J. 0 I don't cry any more than usual
1 I cry more now than I used to
2 I cry all the time now
3 I used to be able to cry but now I can't cry even though I want to

K. 0 I am no more irritated now than I ever am
1 I get annoyed or irritated more easily than I used to
2 I feel irritated all the time now
3 I don't get irritated at all by the things that used to irritate me

L. 0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost most of my interest in other people
3 I have lost all of my interest in other people

M. 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty in making decisions than before
3 I can't make decisions at all any more

N. 0 I don't feel I look any worse than I used to
1 I am worried that I am looking old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly

O. 0 I can work about as well as before
1 It takes extra effort to get started doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

P. 0 I can sleep as well as usual
1 I don't sleep as well as I used to
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

Q. 0 I don't get any more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

R. 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all any more

S. 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds

I am purposely trying to lose weight by eating less. Yes No

T. 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains, or upset stomach, or constipation
2 I am very worried about physical problems and it's hard to think of much else
3 I am so worried about my physical problems I cannot think about anything else

U. 0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

| DATE (MO., DY., YR.) | LOCATION | SERVICE |
|---|---|---|
| AGE | DOCTOR | IF NO PLATE, PRINT NAME, SEX, AND HISTORY NO |

## THE NEW YORK HOSPITAL-CORNELL MEDICAL CENTER

### Consent Form for Clinical Investigation

**Project Title:** PSYCHONEUROENDOCRINE ASSESSMENT IN PSYCHIATRY

**Subject:**_____ **Research Project No.**_____

You are invited to participate in a study of neuroendocrine and cognitive changes in mental illness. Physicians of The New York Hospital and Cornell University Medical College hope to learn how certain hormonal patterns in psychiatric patients relate to intellectual and emotional changes, and how this relationship varies as clinical improvement occurs. You were selected as a possible participant in this study because you may be in a clinical state in which some endocrine functions are temporarily altered.

If you decide to participate, we will do a standard endocrine test called the dexamethasone suppression test (DST) during the first week of the study and in the week prior to your discharge from the hospital. In each of these two (2) DSTs, you will take a small amount of a synthetic cortisone-like drug called dexamethasone at 11PM, and have blood samples drawn at 8AM and 4PM on the day before and the day after dexamethasone. Finally, on the day before each DST, you will be given a comprehensive battery of neuropsychological tests. This battery will include tasks measuring motor speed and dexterity, attention, concentration, memory, and cognitive flexibility. Testing requires approximately 2½ hours and will be divided into two (2) sessions. You will also be asked to complete some brief rating scales of your mood.

Your participation in the project involves the following risks: There are essentially no risks to either the blood tests or the cognitive tests. The DST has been used by endocrinologists for more than 20 years without difficulty. There is the minor discomfort of blood drawing and a bruise can develop at the site of needle insertion. The cognitive and psychomotor tasks have been selected from frequently used neuropsychological procedures.

Benefits derived by you from this research involve more extensive assessment of your mental status during your hospital stay. This will enable us to provide you and your physician with more detailed information about your clinical condition. We cannot and do not guarantee that you will receive any benefits from this study.

No alternative standard diagnostic or treatment procedures that might be advantageous to you are being withheld as a result of this research. Any information obtained during this study and identified with you will remain confidential and will be disclosed only with your permission.

Your decision whether or not to participate will not prejudice your future relations with The New York Hospital-Cornell Medical Center. If you decide to participate, you are free to discontinue participation at any time.

In accordance with Federal regulations, we are obliged to inform you about the Medical Center's policy in the event physical injury occurs. If, as a result of your participation, you experience physical injury from known or unknown risks of the research procedures as described, immediate medical care and treatment,

(continued)

Consent Form for Clinical Investigation (Cont'd.)

including hospitalization if necessary, will be available. No monetary compensation, however, is available and you will be responsible for the costs of such medical treatment, either directly or through your medical insurance and/or other forms of medical coverage. Further information can be obtained by calling (212) 472-8250.

If you have any questions, please ask us. If you have additional questions later, Dr. Peter Stokes or Carolyn Sikes (Payne Whitney Clinic -- Room 277: 472-6430) will be happy to answer them.

You will be offered a copy of this form to keep.

You are making a decision as to whether or not to participate. Your signature indicates that you have read the information provided above and have decided to do so. You may withdraw at any time without prejudice after signing this form should you choose to discontinue participation in this study.

| | | |
|---|---|---|
| | | AM PM |
| Signature | Date | Time |
| | | AM PM |
| Signature of Witness | Date | Time |
| | | AM PM |
| Signature of Investigator | Date | Time |